WHO monographs on

medicinal plants commonly used in the Newly Independent States (NIS)

World Health Organization

WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

World Health Organization

WHO Library Cataloguing-in-Publication Data

WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS).

1.Plants, Medicinal. 2.Medicine, Traditional. 3.Angiosperms. 4.Commonwealth of Independent States. I. World Health Organization.

ISBN 978 92 4 159772 2 (NLM classification: QV 766)

Printed in France

Contents

Acknowledgements

Special acknowledgement is due to Professor Elmira Amroyan of the Scientific Centre of Drug and Medical Technology Expertise, Yerevan, Armenia, and Dr Ain Raal of the Institute of Pharmacy, University of Tartu, Estonia, for drafting and revising the monographs. The photograph for the front cover was also kindly provided by Dr Raal. Similarly, special acknowledgement is due to Dr Raymond Boudet-Dalbin of the Laboratoire de Chimie Thérapeutique, University of Paris, France, for drawing the chemical structures.

WHO also acknowledges with thanks the valuable work of the approximately 120 experts in more than 60 countries who provided comments and advice on the draft texts; those who submitted comments through the World Self-Medication Industry (a nongovernmental organization in official relations with WHO); and those who participated in the WHO Consultation on Medicinal Plants Commonly Used in NIS held in WHO Headquarters, Geneva, Switzerland, in July 2006, to review the monographs (see Annex).

Sincere appreciation is extended to the Nippon Foundation, Japan, which provided funds for the development and publication of this volume.

Finally, WHO wishes to express thanks to Dr Annet Zakaryan, Ann Arbor, USA, for her indispensable assistance in finalizing and editing the manuscripts.

Introduction

Background

The results from the recent WHO/TRM Global Survey on National Policy on Traditional and Complementary/Alternative Medicine and on Regulation of Herbal Medicines in 2003 show that the European herbal medicines market is growing steadily. For example, between 1999 and 2001, herbal medicines sales increased by 22% in the Czech Republic, doubled in Turkmenistan, and increased by 170% in Bulgaria.

Currently, the European market is considered to be the world's largest single commercial market for medicinal plants and herbal medicines. European countries are not just importers, but also producers of a large variety of medicinal plants and herbal medicines. European consumers, for example, in France, Germany, Italy, Sweden, Switzerland and the UK often use herbal medicines to complement treatment with conventional medicines.

In the Newly Independent States (NIS) and Countries of Central and Eastern Europe (CCEE), consumers likewise often favour herbal products, but for a different reason. Difficult economic conditions often limit access to the rather expensive conventional medicines that are available, with the result that they seek out less expensive alternative medicines such as herbal products.

Many European Union countries already have well-established national policies and programmes for regulating and monitoring herbal medicines. Many NIS and CCEE Member States are now similarly striving to develop and implement national policies and programmes to regulate herbal medicines.

Difficulties and needs in the field of herbal medicines in NIS countries

In some NIS and CCEE countries a number of medicinal plants are grown and not only consumed domestically, but also exported to other countries. Indeed, exporting medicinal plants is a principal source of income for some NIS and CCEE countries. Many NIS and CCEE governments are therefore keen to ensure quality control of medicinal plants and me-

dicinal plant materials, so as to maintain and increase the credibility of their products on the international market. However, they often lack technical expertise, skills and knowledge in this area, as well as resources for conducting research and establishing national standards and quality assurance measures for medicinal plants and herbal medicines.

According to the information collected during WHO's recent global survey on traditional medicine:

- nine NIS countries would like WHO to facilitate information sharing between Member States on regulatory issues;
- ten NIS countries would like WHO to provide general guidance on research and evaluation of traditional medicine;
- additional requests included requests for support for national capacity building in establishing national regulation of herbal medicines, and provision via databases of information on herbal medicines.

Some NIS and CCEE countries have developed their own national monographs on herbal medicines, either within national pharmacopoeias or national formularies. These countries include Armenia, Kyrgyzstan, Romania, Slovakia and Uzbekistan. However, since most NIS lack research data and funds, they have been unable to develop their own national monographs.

At the WHO regulatory training workshop for Europe in September 2003, many of the NIS participating national drug regulatory authorities requested assistance from WHO in developing monographs on medicinal plants commonly used in the NIS.

The objectives of development of the monographs for NIS countries

Since 1999, WHO has published four volumes of the WHO monographs on selected medicinal plants, that include 116 monographs. All of these volumes are now available on the WHO web site (http://www.who.int/medicines).

Despite the increasing use of herbal medicines, there is still a significant lack of research data in this field, so that the WHO monographs are playing an increasingly important role. For example, in the recent WHO global survey on national policy and regulation of herbal medicines, of the 34 countries reporting that they do not have their own national monographs and use other monographs, 13 use the WHO monographs as an authoritative reference. Moreover, the format of the WHO monographs continues to be commonly used for developing national monographs. In the same survey, of the 46 countries that have already developed national

monographs on herbal medicines, several countries reported having used the WHO format as a basis.

In order to meet demands of NIS countries to regulate herbal medicines and to ensure safety, efficacy and quality of herbal medicines, WHO has provided technical guidance and worked with the national health authorities of interested NIS and CCEE to develop monographs on commonly-used medicinal plants in the NIS.

The NIS monographs include comprehensive scientific information on the safety, efficacy and quality of medicinal plants. The format of the NIS monographs is the same as of the WHO monographs on medicinal plants. Each monograph follows a standard format, with information presented in two parts, followed by a reference list. The first part presents pharmacopoeial summaries for quality assurance, while the second part includes sections on medicinal uses, pharmacology, safety issues and dosage forms.

Through the participation in the development of the monographs, the objectives are to:

- assist national authorities and experts in NIS and CCEE countries to learn how to develop official monographs on medicinal plants;
- facilitate the national regulatory authorities to build their national capacity in establishing national quality specifications and standards for herbal medicines, national formularies on herbal medicines, as well as quality assurance and control measures for herbal medicines in NIS and CCEE countries;
- promote research on herbal medicines and networking of researchers on herbal medicines within and outside the NIS and CCEE;
- establish a network among the NIS and CCEE to facilitate sharing of information and experience in regulation, research and use of herbal medicines.

Process of the development of the monographs for NIS countries

Firstly WHO worked with the national health authorities and experts of NIS and CCEE countries to establish a working group on development of the monographs. Then they developed a list of monographs on commonly-used medicinal plants in the NIS. The list was finalized by a Working group meeting. It was agreed that there would be a total of 30 to 35 monographs, which would be developed through two mechanisms:

- development of new monographs;

- adoption of existing relevant monographs from the four volumes of WHO monographs on selected medicinal plants and translation into Russian.

Then WHO coordinated collection of relevant research information – not only with the national health authorities and experts of NIS and CCEE countries, but also together with WHO Collaborating Centres for traditional medicine and other research institutions and nongovernmental organizations (NGOs). The experts from NIS and CCEE countries drafted the new monographs, based on the standard format, simultaneously in English and Russian. The draft monographs have been widely circulated to 256 experts and national regulatory authorities in 99 countries, as well as NGOs, for their comments and opinions.

Then, draft new monographs were reviewed and finalized by a WHO Consultation. The participants included the national health authorities and experts of NIS and CCEE countries, as well as experts from WHO Collaborating Centres for traditional medicine and other research institutions and NGOs. Following extensive discussion, 13 of 14 new monographs were approved by the WHO Consultation.

In order to ensure the quality of the monographs, the final version has been reviewed by the experts from the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, IL, USA.

Use of the monographs

The monographs may serve as an authoritative source of information for national drug regulatory authorities, since they have been fully involved in the development of the monographs. However, it should also be emphasized that the descriptions included in the section on medicinal uses should not be taken as implying WHO's official endorsement or approval and also not intended to replace any national monographs or national pharmacopoeia of medicinal plants. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of information exchange.

Dr Xiaorui Zhang
Coordinator
Traditional Medicine
Department of Essential Medicines and Pharmaceutical Policies (EMP)
World Health Organization
Geneva, Switzerland

General technical notices

These WHO monographs are not pharmacopoeial monographs. Their purpose is to provide scientific information on the safety, efficacy and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in WHO's Member States; to provide models to assist WHO's Member States in developing their own monographs or formularies for these and other herbal medicines; and to facilitate information exchange among WHO's Member States.

The format used for this volume essentially follows that of volumes 2, 3 and 4 of *WHO monographs on selected medicinal plants*.

The *Definition* provides the Latin binomial name, the most important criterion in quality assurance. Latin binomial synonyms and vernacular names, listed in *Synonyms* and *Selected vernacular names* respectively, are names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International Code of Botanical Nomenclature. The vernacular names comprise an alphabetical list of selected names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. They refer to the medicinal plant itself not the medicinal plant part, which is identical to the monograph name. The lists are not complete, but reflect the names of the concerned medicinal plant appearing in the official monographs and reference books consulted and those in the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, Chicago, IL, USA). While every effort has been made to delete names referring to the medicinal plant part, the relevant section of each monograph may still include these.

Geographical distribution is not normally found in official compendia, but is included here to provide additional quality assurance information. The detailed botanical description under Description is intended for qual-

ity assurance at the stages of production and collection; the description of the crude drug material under *Plant material of interest* is for the same purpose at the manufacturing and commerce stages.

General identity tests, Purity tests and *Chemical assays* are all normal compendial components included under those headings in these monographs. Where purity tests do not specify accepted limits, those limits should be set in accordance with national requirements by the appropriate authorities of Member States.

Each medicinal plant and the specific plant part used as crude drug material contain active or major chemical constituents with a characteristic profile that can be used for chemical quality control and quality assurance. These constituents are described in the *Major chemical constituents*.

Descriptions included in *Medicinal uses* should not be taken as implying WHO's official endorsement or approval for such uses. They merely represent the systematic collection of scientific information available at the time of preparation, for information exchange.

The first category, *Uses supported by clinical data,* includes medical indications that are well established in some countries and have been validated by clinical studies documented in the scientific literature. Clinical trials may be controlled, randomized, double-blind studies, open trials, cohort studies or well documented observations on therapeutic applications.

The second category, *Uses described in pharmacopoeias and well established documents,* includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or governmental monographs. Uses having a pharmacologically plausible basis are also included, as well as information resulting from clinical studies that clearly need to be repeated because of conflicting results.

The third category, *Uses described in traditional medicine,* refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. Their appropriateness could not be assessed, because sufficient data to support the claims could not be found in the literature. Traditional uses that address severe pathologies, such as cancer, AIDS, hepatitis, etc., as they relate to these modern biomedical terms, should only be included under the third heading if pharmacological data or robust ethnopharmacological/ethnobotanical reports are available to support the claims.

The *Experimental pharmacology* section includes only the results of investigations that prove or disprove the cited medicinal uses. Brief details of the best-performed studies have been included in this section. Other published experimental data that are not associated with the medicinal uses have not been included, to avoid confusion.

The details included in the *References* have been checked against the original sources wherever possible. For references in languages other than English, except for those in Chinese and Japanese, the title is given in the original language, except in cases where an English summary is available.

Bulbus Allii Sativi*

Definition

Bulbus Allii Sativi consists of the fresh or dried bulbs of *Allium sativum* L. (Liliaceae) (*1*, *2*).

Synonyms

Porvium sativum Rehb. (*1*, *3*).

Selected vernacular names

It is most commonly known as "garlic". Ail, ail commun, ajo, akashneem, allium, alubosa elewe, ayo-ishi, ayu, banlasun, camphor of the poor, dai tóan, dasuan, dawang, dra thiam, foom, Gartenlauch, hom khaao, hom kía, hom thiam, hua thiam, kesumphin, kitunguu-sumu, Knoblauch, kra thiam, krathiam, krathiam cheen, krathiam khaao, l'ail, lahsun, lai, lashun, lasan, lasun, lasuna, Lauch, lay, layi, lehsun, lesun, lobha, majo, naharu, nectar of the gods, ninniku, pa-se-waa, poor man's treacle, rason, rasonam, rasun, rustic treacles, seer, skordo, sluôn, stinking rose, sudulunu, ta-suam, ta-suan, tafanuwa, tellagada, tellagaddalu, thiam, toi thum, tum, umbi bawang putih, vallaippundu, velluli, vellulli (*1–13*).

Description

A perennial, erect bulbous herb, 30–60 cm tall, strong smelling when crushed. The underground portion consists of a compound bulb with numerous fibrous rootlets; the bulb gives rise above ground to a number of narrow, keeled, grasslike leaves. The leaf blade is linear, flat, solid, 1.0–2.5 cm wide, 30–60 cm long, and has an acute apex. Leaf sheaths form a pseudostem. Inflorescences are umbellate; scape smooth, round, solid, and coiled at first, subtended by membraneous, long-beaked spathe, splitting on one side and remaining attached to umbel. Small bulbils are produced in inflorescences; flowers are variable in number and sometimes absent, seldom open and may wither in bud. Flowers are on slender

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.

pedicels; consisting of perianth of 6 segments, about 4–6 mm long, pinkish; stamens 6, anthers exserted; ovary superior, 3-locular. Fruit is a small loculicidal capsule. Seeds are seldom if ever produced (*8*, *9*).

Plant material of interest: fresh or dried bulbs

General appearance

Bulbus Allii Sativi consists of several outer layers of thin sheathing protective leaves which surround an inner sheath. The latter enclose the swollen storage leaves called "cloves". Typically, the bulb possesses a dozen sterile sheathing leaves within which are 6–8 cloves bearing buds making a total of 10–20 cloves and 20–40 well-developed but short and embedded roots. The cloves are asymmetric in shape, except for those near the centre (*1*).

Organoleptic properties

Odour strong, characteristic alliaceous (*1*, *6*, *8*); taste very persistently pungent and acrid (*1*, *6*, *8*).

Microscopic characteristics

The bulbs show a number of concentric bulblets; each is 5–10 mm in diameter and consists of an outer scale, an epidermis enclosing a mesophyll free from chlorophyll, a ground tissue and a layer of lower epidermal cells. Dry scales consist of 2 or 3 layers of rectangular cells having end walls with a broadly angular slant. These cells contain many rhomboid crystals of calcium oxalate. The upper epidermal cells next to the dry scale layer consist of a single layer of rectangular to cubical cells next to which are several layers of large parenchymatous cells. Among these cells are interspaced many vascular bundles, each of which consists of xylem and phloem arranged alternately. Lower epidermis consists of cubical cells which are much smaller than the upper epidermal cells. The same arrangement of tissues is met within different bulblets, 2 or 3 of which are arranged concentrically (*1*, *6*).

Powdered plant material

Pale buff to greyish or purplish white, with characteristic aromatic alliaceous odour and taste. It is characterized by the presence of sclereids of the epidermis of protective leaves, thin epidermis of storage cells, latex tubes, swollen parenchyma cells with granular contents, and lignified narrow spiral and annular vessels (*1*).

Geographical distribution

Bulbus Allii Sativi is probably indigenous to Asia (*1*, *7*), but it is commercially cultivated in most countries.

General identity tests

Macroscopic and microscopic examinations and microchemical analysis are used to identify organic sulfur compounds (*1*), thin-layer chromatographic analysis to determine the presence of alliin (*14*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Bulbus Allii Sativi products should be negative. The maximum acceptable limits of other microorganisms are as follows (*2*, *15*, *16*). Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 5.0% (*2*).

Acid-insoluble ash

Not more than 1.0% (*4*).

Water-soluble extractive

Not less than 5.0% (*4*).

Alcohol-soluble extractive

Not less than 4.0% (*4*).

Moisture

Not more than 7% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Bulbus Allii Sativi is not more than 0.05 mg/kg (*2*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*15*) and guidelines for predicting dietary intake of pesticide residues (*17*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*15*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*15*).

Other purity tests

Chemical tests and tests for foreign organic matter to be established in accordance with national requirements.

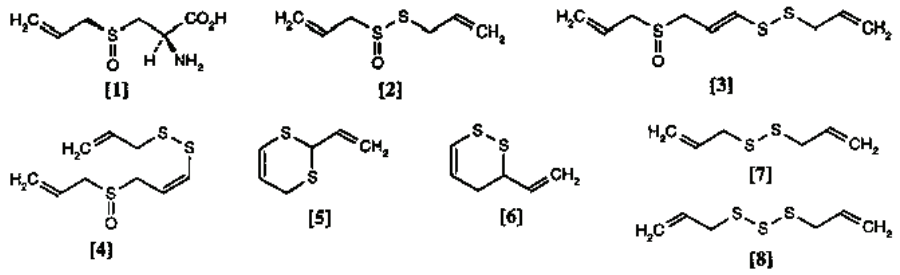
Chemical assays

Qualitative and quantitative assay for sulfur constituents (alliin, allicin etc.) content by means of high-performance liquid chromatography (*18–22*) or gas chromatography–mass spectroscopy (*23*) methods.

Major chemical constituents

The most important chemical constituents reported from Bulbus Allii Sativi are the sulfur compounds (*7*, *9*, *24*, *25*). It has been estimated that cysteine sulfoxides (e.g. alliin [**1**]) and the non-volatile γ-glutamylcysteine peptides make up more than 82% of the total sulfur content of garlic (*25*).

The thiosulfinates (e.g. allicin [**2**]), ajoenes (e.g. *E*-ajoene [**3**], *Z*-ajoene [**4**]), vinyldithiins (e.g. 2-vinyl-(4*H*)-1,3-dithiin [**5**], 3-vinyl-(4*H*)-1,2-dithiin [**6**]), and sulfides (e.g. diallyl disulfide [**7**], diallyl trisulfide [**8**]), however, are not naturally occurring compounds. Rather, they are degradation products from the naturally occurring cysteine sulfoxide, alliin [**1**]. When the garlic bulb is crushed, minced, or otherwise processed, alliin is released from compartments and interacts with the enzyme alliinase in adjacent vacuoles. Hydrolysis and immediate condensation of the reactive intermediate (allylsulfenic acid) forms allicin [**2**]. One milligram of alliin is considered to be equivalent to 0.45 mg of allicin (*26*). Allicin itself is an unstable product and will undergo additional reactions to form other derivatives (e.g. products [**3**]–[**8**]), depending on environmental and processing conditions (*24–26*). Extraction of garlic cloves with ethanol at <0 °C gave alliin [**1**]; extraction with ethanol and water at 25 °C led to allicin [**2**] and no alliin; and steam distillation (100 °C) converted the alliin totally to diallyl sulfides [**7**], [**8**] (*24*, *25*). Sulfur chemical profiles of Bulbus Allii Sativi products reflected the processing procedure: bulb, mainly



alliin, allicin; dry powder, mainly alliin, allicin; volatile oil, almost entirely diallyl sulfide, diallyl disulfide, diallyl trisulfide, and diallyl tetrasulfide; oil macerate, mainly 2-vinyl-[4*H*]-1,3-dithiin, 3-vinyl-[4*H*]-1,3-dithiin, *E*-ajoene, and *Z*-ajoene (*18–22*, *24*). The content of alliin was also affected by processing treatment: whole garlic cloves (fresh) contained 0.25–1.15% alliin, while material carefully dried under mild conditions contained 0.7–1.7% alliin (*18–21*).

Gamma-glutamylcysteine peptides are not acted on by alliinase. On prolonged storage or during germination, these peptides are acted on by γ-glutamyl transpeptidase to form thiosulfinates (*25*).

Dosage forms

Fresh bulbs, dried powder, volatile oil, oil macerates, juice, aqueous or alcoholic extracts, aged garlic extracts (minced garlic that is incubated in aqueous alcohol (15–20%) for 20 months, then concentrated), and odourless garlic products (garlic products in which the alliinase has been inactivated by cooking; or in which chlorophyll has been added as a deodorant; or aged garlic preparations that have low concentrations of water-soluble sulfur compounds) (*18*, *24*).

The juice is the most unstable dosage form. Alliin and allicin decompose rapidly, and those products must be used promptly (*18*).

Dried Bulbus Allii Sativi products should be stored in well-closed containers, protected from light, moisture, and elevated temperature.

Medicinal uses

Uses supported by clinical data

As an adjuvant to dietetic management in the treatment of hyperlipidaemia, and in the prevention of atherosclerotic (age-dependent) vascular changes (*5*, *27–31*). The drug may be useful in the treatment of mild hypertension (*11*, *28*).

Uses described in pharmacopoeias and in traditional systems of medicine

The treatment of respiratory and urinary tract infections, ringworm and rheumatic conditions (*1*, *4*, *7*, *9*, *11*). The herb has been used as a carminative in the treatment of dyspepsia (*32*).

Uses described in folk medicine, not supported by experimental or clinical data

As an aphrodisiac, antipyretic, diuretic, emmenagogue, expectorant, and sedative, to treat asthma and bronchitis, and to promote hair growth (*6*, *9*, *13*).

Pharmacology

Experimental pharmacology

Bulbus Allii Sativi has a broad range of antibacterial and antifungal activity (*13*). The essential oil, water, and ethanol extracts, and the juice inhibit the in vitro growth of *Bacillus* species, *Staphylococcus aureus*, *Shigella sonnei*, *Erwinia carotovora*, *Mycobacterium tuberculosis*, *Escherichia coli*, *Pasteurella multocida*, *Proteus* species, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Candida* species, *Cryptococcus* species, *Rhodotorula rubra*, *Toruloposis* species, *Trichosporon pullulans*, and *Aspergillus niger* (*33–40*). Its antimicrobial activity has been attributed to allicin, one of the active constituents of the drug (*41*). However, allicin is a relatively unstable and highly reactive compound (*37*, *42*) and may not have antibacterial activity in vivo. Ajoene and diallyl trisulfide also have antibacterial and antifungal activities (*43*). Garlic has been used in the treatment of roundworm (*Ascaris strongyloides*) and hookworm (*Ancylostoma caninum* and *Necator americanus*) (*44*, *45*). Allicin appears to be the active anthelminthic constituent, and diallyl disulfide was not effective (*46*).

Fresh garlic, garlic juice, aged garlic extracts, or the volatile oil all lowered cholesterol and plasma lipids, lipid metabolism, and atherogenesis both in vitro and in vivo (*18*, *43*, *47–64*). In vitro studies with isolated primary rat hepatocytes and human HepG2 cells have shown that water-soluble garlic extracts inhibited cholesterol biosynthesis in a dose-dependent manner (*48–50*). Antihypercholesterolaemic and antihyperlipidaemic effects were observed in various animal models (rat, rabbit, chicken, pig) after oral (in feed) or intragastric administration of minced garlic bulbs; water, ethanol, petroleum ether, or methanol extracts; the essential oil; aged garlic extracts and the fixed oil (*51–64*). Oral administration of allicin to rats during a 2-month period lowered serum and liver levels of total lipids, phospholipids, triglycerides, and total cholesterol (*65*). Total plasma lipids and cholesterol in rats were reduced after intraperitoneal

injection of a mixture of diallyl disulfide and diallyl trisulfide (*66*). The mechanism of garlic's antihypercholesterolaemic and antihyperlipidaemic activity appears to involve the inhibition of hepatic hydroxymethylglutaryl-CoA (HMG-CoA) reductase and remodelling of plasma lipoproteins and cell membranes (*67*). At low concentrations (<0.5 mg/ml), garlic extracts inhibited the activity of hepatic HMG-CoA reductase, but at higher concentrations (>0.5 mg/ml) cholesterol biosynthesis was inhibited in the later stages of the biosynthetic pathway (*68*). Alliin was not effective, but allicin and ajoene both inhibited HMG-CoA reductase in vitro (IC_{50} = 7 and 9 mmol/l respectively) (*49*). Because both allicin and ajoene are converted to allyl mercaptan in the blood and never reach the liver to affect cholesterol biosynthesis, this mechanism may not be applicable in vivo. In addition to allicin and ajoene, allyl mercaptan (50 mmol/l) and diallyl disulfide (5 mmol/l) enhanced palmitate-induced inhibition of cholesterol biosynthesis in vitro (*50*). It should be noted that water extracts of garlic probably do not contain any of these compounds; therefore other constituents of garlic, such as nicotinic acid and adenosine, which also inhibit HMG-CoA reductase activity and cholesterol biosynthesis, may be involved (*69*, *70*).

The antihypertensive activity of garlic has been demonstrated in vivo. Oral or intragastric administration of minced garlic bulbs, or alcohol or water extracts of the drug, lowered blood pressure in dogs, guinea-pigs, rabbits, and rats (*52*, *71–73*). The drug appeared to decrease vascular resistance by directly relaxing smooth muscle (*74*). The drug appears to change the physical state functions of the membrane potentials of vascular smooth muscle cells. Both aqueous garlic and ajoene induced membrane hyperpolarization in the cells of isolated vessel strips. The potassium channels opened frequently causing hyperpolarization, which resulted in vasodilation because the calcium channels were closed (*75*, *76*). The compounds that produce the hypotensive activity of the drug are uncertain. Allicin does not appear to be involved (*43*), and adenosine has been postulated as being associated with the activity of the drug. Adenosine enlarges the peripheral blood vessels, allowing the blood pressure to decrease, and is also involved in the regulation of blood flow in the coronary arteries; however, adenosine is not active when administered orally. Bulbus Allii Sativi may increase production of nitric oxide, which is associated with a decrease in blood pressure. In vitro studies using water or alcohol extracts of garlic or garlic powder activated nitric-oxide synthase (*77*), and these results have been confirmed by in vivo studies (*78*).

Aqueous garlic extracts and garlic oil have been shown in vivo to alter the plasma fibrinogen level, coagulation time, and fibrinolytic activity

(*43*). Serum fibrinolytic activity increased after administration of dry garlic or garlic extracts to animals that were artificially rendered arteriosclerotic (*79*, *80*). Although adenosine was thought to be the active constituent, it did not affect whole blood (*43*).

Garlic inhibited platelet aggregation in both in vitro and in vivo studies. A water, chloroform, or methanol extract of the drug inhibited collagen-, ADP-, arachidonic acid-, epinephrine-, and thrombin-induced platelet aggregation in vitro (*81–87*). Prolonged administration (intragastric, 3 months) of the essential oil or a chloroform extract of Bulbus Allii Sativi inhibited platelet aggregation in rabbits (*88–90*). Adenosine, alliin, allicin, and the transformation products of allicin, the ajoenes; the vinyldithiins; and the dialkyloligosulfides are responsible for inhibition of platelet adhesion and aggregation (*4*, *42*, *91–93*). In addition methyl allyl trisulfide, a minor constituent of garlic oil, inhibited platelet aggregation at least 10 times as effectively than allicin (*94*). Inhibition of the arachidonic acid cascade appears to be one of the mechanisms by which the various constituents and their metabolites affect platelet aggregation. Inhibition of platelet cyclic AMP phosphodiesterase may also be involved (*91*).

Ajoene, one of the transformation products of allicin, inhibited in vitro platelet aggregation induced by the platelet stimulators—ADP, arachidonic acid, calcium ionophore A23187, collagen, epinephrine, platelet activating factor, and thrombin (*95*, *96*). Ajoene inhibited platelet aggregation in cows, dogs, guinea-pigs, horses, monkeys, pigs, rabbits, and rats (*95*, *96*). The antiplatelet activity of ajoene is potentiated by prostacyclin, forskolin, indometacin, and dipyridamole (*95*). The mechanism of action involves the inhibition of the metabolism of arachidonic acid by both cyclooxygenase and lipoxygenase, thereby inhibiting the formation of thromboxane A2 and 12-hydroxyeicosatetraenoic acid (*95*). Two mechanisms have been suggested for ajoene's antiplatelet activity. First, ajoene may interact with the primary agonist–receptor complex with the exposure of fibrinogen receptors through specific G-proteins involved in the signal transduction system on the platelet membrane (*92*). Or it may interact with a haemoprotein involved in platelet activation that modifies the binding of the protein to its ligands (*96*).

Hypoglycaemic effects of Bulbus Allii Sativi have been demonstrated in vivo. Oral administration of an aqueous, ethanol, petroleum ether, or chloroform extract, or the essential oil of garlic, lowered blood glucose levels in rabbits and rats (*24*, *97–104*). However, three similar studies reported negative results (*105– 107*). In one study, garlic bulbs administered orally (in feed) to normal or streptozotocin-diabetic mice reduced hyperphagia and polydipsia but had no effect on hyperglycaemia or hypoinsu-

linaemia (*107*). Allicin administered orally to alloxan-diabetic rats lowered blood glucose levels and increased insulin activity in a dose-dependent manner (*24*). Garlic extract's hypoglycaemic action appears to enhance insulin production, and allicin has been shown to protect insulin against inactivation (*108*).

Intragastric administration of an ethanol extract of Bulbus Allii Sativi decreased carrageenin-induced rat paw oedema at a dose of 100 mg/kg. The antiinflammatory activity of the drug appears to be due to its antiprostaglandin activity (*109*, *110*).

A water or ethanol extract of the drug showed antispasmodic activity against acetylcholine, prostaglandin E2 and barium-induced contractions in guinea-pig small intestine and rat stomach (*111*). The juice of the drug relaxed smooth muscle of guinea-pig ileum, rabbit heart and jejunum, and rat colon and fundus (*112*, *113*). The juice also inhibited norepinephrine-, acetylcholine- and histamine-induced contractions in guinea-pig and rat aorta, and in rabbit trachea (*112*, *113*).

Clinical pharmacology

The efficacy of Bulbus Allii Sativi as a carminative has been demonstrated in human studies. A clinical study of 29 patients taking two tablets daily (~1000 mg/day) of a dried garlic preparation demonstrated that garlic relieved epigastric and abdominal distress, belching, flatulence, colic, and nausea, as compared with placebo (*32*). It was concluded that garlic sedated the stomach and intestines, and relaxed spasms, retarded hyperperistalsis, and dispersed gas (*32*).

A meta-analysis of the effect of Bulbus Allii Sativi on blood pressure reviewed a total of 11 randomized, controlled trials (published and unpublished) (*113*, *114*). Each of the trials used dried garlic powder (tablets) at a dose of 600–900 mg daily (equivalent to 1.8–2.7 g/day fresh garlic). The median duration of the trials was 12 weeks. Eight of the trials with data from 415 subjects were included in the analysis; three trials were excluded owing to a lack of data. Only three of the trials specifically used hypertensive subjects, and many of the studies suffered from methodological flaws. Of the seven studies that compared garlic with placebo, three reported a decrease in systolic blood pressure, and four studies reported a decrease in diastolic blood pressure (*115*). The results of the meta-analysis led to the conclusion that garlic may have some clinical use-fulness in mild hypertension, but there is still insufficient evidence to recommend the drug as a routine clinical therapy for the treatment of hypertension (*115*).

A meta-analysis of the effects of Bulbus Allii Sativi on serum lipids and lipoproteins reviewed 25 randomized, controlled trials (published

and unpublished) (*116*) and selected 16 with data from 952 subjects to include in the analysis. Fourteen of the trials used a parallel group design, and the remaining two were cross-over studies. Two of the studies were conducted in an open-label fashion, two others were single-blind, and the remainder were double-blind. The total daily dose of garlic was 600–900 mg of dried garlic powder, or 10 g of raw garlic, or 18 mg of garlic oil, or aged garlic extracts (dosage not stated). The median duration of the therapy was 12 weeks. Overall, the subjects receiving garlic supplementation (powder or non-powder) showed a 12% reduction (average) in total cholesterol, and a 13% reduction (powder only) in serum triglycerides. Meta-analysis of the clinical studies confirmed the lipid-lowering action of garlic. However, the authors concluded that the overall quality of the clinical trials was poor and that favourable results of better-designed clinical studies should be available before garlic can be routinely recommended as a lipid-lowering agent. However, current available data support the hypothesis that garlic therapy is at least beneficial (*116*). Another metaanalysis of the controlled trials of garlic's effects on total serum cholesterol reached similar conclusions (*117*). A systematic review of the lipid-lowering potential of a dried garlic powder preparation in eight studies with 500 subjects had similar findings (*118*). In seven of the eight studies reviewed, a daily dose of 600–900 mg of garlic powder reduced serum cholesterol and triglyceride levels by 5–20%. The review concluded that garlic powder preparations do have lipid-lowering potential (*118*).

An increase in fibrinolytic activity in the serum of patients suffering from atherosclerosis was observed after administration of aqueous garlic extracts, the essential oil, and garlic powder (*119*, *120*). Clinical studies have demonstrated that garlic activates endogenous fibrinolysis, that the effect is detectable for several hours after administration of the drug, and that the effect increases as the drug is taken regularly for several months (*43*, *121*). Investigations of the acute haemorheological (blood flow) effect of 600–1200 mg of dry garlic powder demonstrated that the drug decreased plasma viscosity, tissue plasminogen activator activity and the haematocrit level (*118*).

The effects of the drug on haemorheology in conjunctival vessels was determined in a randomized, placebo-controlled, double-blind, cross-over trial. Garlic powder (900 mg) significantly increased the mean diameter of the arterioles (by 4.2%) and venules (by 5.9%) as compared with controls (*122*). In another double-blind, placebo-controlled study, patients with stage II peripheral arterial occlusive disease were given a daily dose of 800 mg of garlic powder for 4 weeks (*123*, *124*). Increased capil-

lary erythrocyte flow rate and decreased plasma viscosity and plasma fibrinogen levels were observed in the group treated with the drug (*123*, *124*). Determinations of platelet aggregation *ex vivo*, after ingestion of garlic and garlic preparations by humans, suffer from methodological difficulties that may account for the negative results in some studies (*24*). In one study in patients with hypercholesterolinaemia treated with a garlic–oil macerate for 3 months, platelet adhesion and aggregation decreased significantly (*125*). In a 3-year intervention study, 432 patients with myocardial infarction were treated with either an ether-extracted garlic oil (0.1 mg/kg/day, corresponding to 2 g fresh garlic daily) or a placebo (*126*). In the group treated with garlic, there were 35% fewer new heart attacks and 45% fewer deaths than in the control group. The serum lipid concentrations of the treated patients were also reduced (*126*).

The acute and chronic effects of garlic on fibrinolysis and platelet aggregation in 12 healthy patients in a randomized, double-blind, placebo-controlled cross-over study were investigated (*30*). A daily dose of 900 mg of garlic powder for 14 days significantly increased tissue plasminogen activator activity as compared with placebo (*30*). Furthermore, platelet aggregation induced by adenosine diphosphate and collagen was significantly inhibited 2 and 4 hours after garlic ingestion and remained lower for 7 to 14 days after treatment (*30*). Another randomized, double-blind, placebo-controlled study investigated the effects of garlic on platelet aggregation in 60 subjects with increased risk of juvenile ischaemic attack (*29*). Daily ingestion of 800 mg of powdered garlic for 4 weeks significantly decreased the percentage of circulating platelet aggregates and spontaneous platelet aggregation as compared with the placebo group (*29*).

Oral administration of garlic powder (800 mg/day) to 120 patients for 4 weeks in a double-blind, placebo-controlled study decreased the average blood glucose by 11.6% (*30*). Another study found no such activity after dosing noninsulin-dependent patients with 700 mg/day of a spray-dried garlic preparation for 1 month (*127*).

Contraindications

Bulbus Allii Sativi is contraindicated in patients with a known allergy to the drug. The level of safety for Bulbus Allii Sativi is reflected by its worldwide use as a seasoning in food.

Warnings

Consumption of large amounts of garlic may increase the risk of postoperative bleeding (*128*, *129*).

Precautions

Drug interactions

Patients on warfarin therapy should be warned that garlic supplements may increase bleeding times. Blood clotting times have been reported to double in patients taking warfarin and garlic supplements (*130*).

Carcinogenesis, mutagenesis, impairment of fertility

Bulbus Allii Sativi is not mutagenic in vitro (*Salmonella* microsome reversion assay and *Escherichia coli*) (*131*, *132*).

Pregnancy: non-teratogenic effects

There are no objections to the use of Bulbus Allii Sativi during pregnancy and lactation.

Nursing mothers

Excretion of the components of Bulbus Allii Sativi into breast milk and its effect on the newborn has not been established.

Other precautions

No general precautions have been reported, and no precautions have been reported concerning drug and laboratory test interactions, paediatric use, or teratogenic or non-teratogenic effects on pregnancy.

Adverse reactions

Bulbus Allii Sativi has been reported to evoke occasional allergic reactions such as contact dermatitis and asthmatic attacks after inhalation of the powdered drug (*133*). Those sensitive to garlic may also have a reaction to onion or tulip (*133*). Ingestion of fresh garlic bulbs, extracts, or oil on an empty stomach may occasionally cause heartburn, nausea, vomiting, and diarrhoea. Garlic odour from breath and skin may be perceptible (*7*). One case of spontaneous spinal epidural haematoma, which was associated with excessive ingestion of fresh garlic cloves, has been reported (*134*).

Posology

Unless otherwise prescribed, average daily dose is as follows (*7*): fresh garlic, 2–5 g; dried powder, 0.4–1.2 g; oil, 2–5 mg; extract, 300–1000 mg (as solid material). Other preparations should correspond to 4–12 mg of alliin or about 2–5 mg of allicin).

Bulbus Allii Sativi should be taken with food to prevent gastrointestinal upset.

References

1. *African pharmacopoeia*, *Vol. 1*, 1st ed. Lagos, Organization of African Unity, Scientific, Technical & Research Commission, 1985.
2. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1997.
3. Iwu MM. *Handbook of African medicinal plants*. Boca Raton, FL, CRC Press, 1993:111–113.
4. *Materia medika Indonesia*, Jilid VI. Jakarta, Departemen Kesehatan, Republik Indonesia, 1995.
5. *British herbal pharmacopoeia*, *Vol. 1*. London, British Herbal Medicine Association, 1990.
6. *The Indian pharmaceutical codex. Vol. I. Indigenous drugs*. New Delhi, Council of Scientific & Industrial Research, 1953:8–10.
7. Bradley PR, ed. *British herbal compendium*, *Vol. 1*. Bournemouth, British Herbal Medicine Association, 1992.
8. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, Blakiston, 1950: 182–183.
9. Farnsworth NR, Bunyapraphatsara N, eds. *Thai medicinal plants*. Bangkok, Prachachon, 1992:210–287.
10. Kapoor LD. *Handbook of Ayurvedic medicinal plants*. Boca Raton, FL, CRC Press, 1990:26.
11. Hsu HY. *Oriental materia medica, a concise guide*. Long Beach, CA, Oriental Healing Arts Institute, 1986:735–736.
12. Olin BR, ed. Garlic. In: *The Lawrence review of natural products*. St. Louis, MO, Facts and Comparisons, 1994:1–4.
13. *Medicinal plants in Viet Nam*. Manila, World Health Organization, 1990 (WHO Regional Publications, Western Pacific Series, No. 3).
14. Wagner H, Bladt S, Zgainski EM. *Plant drug analysis.* Berlin, SpringerVerlag, 1984:253–257.
15. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
16. *Deutsches Arzneibuch 1996. Vol. 2. Methoden der Biologie*. Stuttgart, Deutscher Apotheker Verlag, 1996.
17. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (unpublished document WHO/FSF/FOS/97.7; available from Food Safety, WHO, 1211 Geneva 27, Switzerland).
18. Lawson LD et al. HPLC analysis of allicin and other thiosulfinates in garlic clove homogenates. *Planta medica*, 1991, 57:263–270.
19. Iberl B et al. Quantitative determination of allicin and alliin from garlic by HPLC. *Planta medica*, 1990, 56:320–326.
20. Ziegler SJ, Sticher O. HPLC of *S*-alk(en)yl-l-cysteine derivatives in garlic including quantitative determination of (+)-*S*-allyl-l-cysteine sulfoxide (alliin). *Planta medica*, 1989, 55:372–378.

21. Mochizuki E et al. Liquid chromatographic determination of alliin in garlic and garlic products. *Journal of chromatography*, 1988, 455:271–277.
22. Freeman F, Kodera Y. Garlic chemistry: Stability of *S*-(2-propenyl)2-propene-1-sulfinothioate (allicin) in blood, solvents and simulated physiological fluids. *Journal of agriculture and food chemistry*, 1995, 43:2332–2338.
23. Weinberg DS et al. Identification and quantification of organosulfur compliance markers in a garlic extract. *Journal of agriculture and food chemistry*, 1993, 41:37–41.
24. Reuter HD, Sendl A. *Allium sativum* and *Allium ursinum*: Chemistry, pharmacology, and medicinal applications. In: Wagner H, Farnsworth NR, eds. *Economic and medicinal plants research*, *Vol. 6.* London, Academic Press, 1994:55–113.
25. Sendl A. *Allium sativum* and *Allium ursinum*, Part 1. Chemistry, analysis, history, botany. *Phytomedicine*, 1995, 4:323–339.
26. Block E. The chemistry of garlic and onions. *Scientific American*, 1985, 252:94–99.
27. German Commission E Monograph, Allii sativi bulbus. *Bundesanzeiger*, 1988, 122:6 June.
28. Auer W, Eiber A, Hertkorn E. Hypertension and hyperlipidemia: garlic helps in mild cases. *British journal of clinical practice*, 1990, 44:3–6.
29. Kiesewetter H et al. Effect of garlic on platelet aggregation in patients with increased risk of juvenile ischaemic attack. *European journal of clinical pharmacology*, 1993, 45:333–336.
30. Kiesewetter H et al. Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. *International journal of clinical pharmacology, therapy and toxicology*, 1991, 29:151–155.
31. Legnani C et al. Effects of dried garlic preparation on fibrinolysis and platelet aggregation in healthy subjects. *Arzneimittel-Forschung*, 1993, 43:119–121.
32. Damrau F, Ferguson EA. The modus operandi of carminatives. *Review of gastroenterology*, 1949, 16:411–419.
33. Fitzpatrick FK. Plant substances active against *Mycobacterium tuberculosis*. *Antibiotics and chemotherapy*, 1954, 4:528–529.
34. Sharma VD et al. Antibacterial property of *Allium sativum.* In vivo and in vitro studies. *Indian journal of experimental biology*, 1980, 15:466–469.
35. Arunachalam K. Antimicrobial activity of garlic, onion and honey. *Geobios*, 1980, 71:46–47.
36. Moore GS, Atkins RD. The antifungistatic effects of an aqueous garlic extract on medically important yeast-like fungi. *Mycologia*, 1977, 69:341–345.
37. Caporaso N, Smith SM, Eng RHK. Antifungal activity in human urine and serum after ingestion of garlic (*Allium sativum*). *Antimicrobial agents and chemotherapy*, 1983, 5:700–702.

38. Abbruzzese MR, Delaha EC, Garagusi VF. Absence of antimycobacterial synergism between garlic extract and antituberculosis drugs. *Diagnosis and microbiology of infectious diseases*, 1987, 8:79–85.
39. Chaiyasothi T, Rueaksopaa V. Antibacterial activity of some medicinal plants. *Undergraduate special project report*, 1975, 75:1–109.
40. Sangmahachai K. *Effect of onion and garlic extracts on the growth of certain bacteria* [Thesis]. Thailand, University of Bangkok, 1978:1–88.
41. Farbman et al. Antibacterial activity of garlic and onions: a historical perspective. *Pediatrics infectious disease journal*, 1993, 12:613–614.
42. Lawson LD, Hughes BG. Inhibition of whole blood platelet-aggregation by compounds in garlic clove extracts and commercial garlic products. *Thrombosis research*, 1992, 65:141–156.
43. Koch HP, Lawson LD, eds. *Garlic, the science and therapeutic application of Allium sativum l. and related species*. Baltimore, Williams and Wilkins, 1996.
44. Kempski HW. Zur kausalen Therapie chronischer Helminthen-Bronchitis. *Medizinische Klinik*, 1967, 62:259–260.
45. Soh CT. The effects of natural food-preservative substances on the development and survival of intestinal helminth eggs and larvae. II. Action on *Ancylostoma duodenale* larvae. *American journal of tropical medicine and hygiene*, 1960, 9:8–10.
46. Araki M et al. Anthelminthics. *Yakugaku zasshi*, 1952, 72:979–982.
47. Mader FH. Treatment of hyperlipidemia with garlic-powder tablets. Evidence from the German Association of General Practitioner's multicentric placebo-controlled, double-blind study. *Arzneimittel-Forschung*, 1990, 40:1111–1116.
48. Gebhardt R. Multiple inhibitory effects of garlic extracts on cholesterol biosynthesis in hepatocytes. *Lipids*, 1993, 28:613–619.
49. Gebhardt R, Beck H, Wagner KG. Inhibition of cholesterol biosynthesis by allicin and ajoene in rat hepatocytes and HepG2 cells. *Biochimica biophysica acta*, 1994, 1213:57–62.
50. Gebhardt R. Amplification of palmitate-induced inhibition of cholesterol biosynthesis in cultured rat hepatocytes by garlic-derived organosulfur compounds. *Phytomedicine*, 1995, 2:29–34.
51. Yeh YY, Yeh SM. Garlic reduces plasma lipids by inhibiting hepatic cholesterol and triacylglycerol synthesis. *Lipids*, 1994, 29:189–193.
52. Petkov V. Pharmacological and clinical studies of garlic. *Deutsche Apotheker Zeitung*, 1966, 106:1861–1867.
53. Jain RC. Onion and garlic in experimental cholesterol induced atherosclerosis. *Indian journal of medical research*, 1976, 64:1509–1515.
54. Qureshi AA et al. Inhibition of cholesterol and fatty acid biosynthesis in liver enzymes and chicken hepatocytes by polar fractions of garlic. *Lipids*, 1983, 18:343–348.
55. Thiersch H. The effect of garlic on experimental cholesterol arteriosclerosis of rabbits. *Zeitschrift für die gesamte experimentelle Medizin*, 1936, 99:473–477.

56. Zacharias NT et al. Hypoglycemic and hypolipidemic effects of garlic in sucrose fed rabbits. *Indian journal of physiology and pharmacology*, 1980, 24:151–154.
57. Gupta PP, Khetrapal P, Ghai CL. Effect of garlic on serum cholesterol and electrocardiogram of rabbit consuming normal diet. *Indian journal of medical science*, 1987, 41:6–11.
58. Mand JK et al. Role of garlic (*Allium sativum*) in the reversal of atherosclerosis in rabbits. In: *Proceedings of the Third Congress of the Federation of Asian and Oceanian Biochemists*. Bangkok, 1983:79.
59. Sodimu O, Joseph PK, Angusti KT. Certain biochemical effects of garlic oil on rats maintained on high fat–high cholesterol diet. *Experientia*, 1984, 40:78–79.
60. Kamanna VS, Chandrasekhara N. Effect of garlic (*Allium sativum* Linn.) on serum lipoproteins and lipoprotein cholesterol levels in albino rats rendered hypercholesteremic by feeding cholesterol. *Lipids*, 1982, 17:483–488.
61. Kamanna VS, Chandrasekhara N. Hypocholesterolic activity of different fractions of garlic. *Indian journal of medical research*, 1984, 79:580–583.
62. Chi MS. Effects of garlic products on lipid metabolism in cholesterol-fed rats. *Proceedings of the Society of Experimental Biology and Medicine*, 1982, 171:174–178.
63. Qureshi AA et al. Influence of minor plant constituents on porcine hepatic lipid metabolism. *Atherosclerosis*, 1987, 64:687–688.
64. Lata S et al. Beneficial effects of *Allium sativum*, *Allium cepa*, and *Commiphora mukul* on experimental hyperlipidemia and atherosclerosis: a comparative evaluation. *Journal of postgraduate medicine*, 1991, 37:132–135.
65. Augusti KT, Mathew PT. Lipid lowering effect of allicin (diallyl disulfide-oxide) on long-term feeding to normal rats. *Experientia*, 1974, 30:468–470.
66. Pushpendran CK et al. Cholesterol-lowering effects of allicin in suckling rats. *Indian journal of experimental biology*, 1980, 18:858–861.
67. Brosche T, Platt D. Garlic. *British medical journal*, 1991, 303, 785.
68. Beck H, Wagnerk G. Inhibition of cholesterol biosynthesis by allicin and ajoene in rat hepatocytes and Hep62 cells. *Biochimica biophysica acta*, 1994, 1213:57–62.
69. Platt D, Brosche T, Jacob BG. Cholesterin-senkende Wirkung von Knoblauch? *Deutsche Medizinische Wochenschrift*, 1992, 117:962–963.
70. Grünwald J. Knoblauch: Cholesterinsenkende Wirkung doppelblind nachgewiesen. *Deutsche Apotheker Zeitung*, 1992, 132:1356.
71. Ogawa H et al. Effect of garlic powder on lipid metabolism in stroke-prone spontaneously hypertensive rats. *Nippon eiyo, shokuryo gakkaishi*, 1993, 46:417– 423.
72. Sanfilippo G, Ottaviano G. Pharmacological investigations on *Allium sativum*. I. General action. II. Action on the arterial pressure and on the respiration. *Bollettino Societa Italiana Biologia Sperimentale*, 1944, 19:156–158.

73. Foushee DB, Ruffin J, Banerjee U. Garlic as a natural agent for the treatment of hypertension: A preliminary report. *Cytobios*, 1982:145–152.
74. Ozturk Y et al. Endothelium-dependent and independent effects of garlic on rat aorta. *Journal of ethnopharmacology*, 1994, 44:109–116.
75. Siegel G et al. Potassium channel activation, hyperpolarization, and vascular relaxation. *Zeitschrift für Kardiologie*, 1991, 80:9–24.
76. Siegel G et al. Potassium channel activation in vascular smooth muscle. In: Frank GB, ed. *Excitation-contraction coupling in skeletal, cardiac, and smooth muscle*. New York, Plenum Press, 1992:53–72.
77. Das I, Khan NS, Sooranna SR. Nitric oxide synthetase activation is a unique mechanism of garlic action. *Biochemical Society transactions*, 1995, 23:S136.
78. Das I, Khan NS, Sooranna SR. Potent activation of nitric oxide synthetase by garlic: a basis for its therapeutic applications. *Current medical research opinion*, 1995, 13:257– 263.
79. Bordia A et al. Effect of essential oil of onion and garlic on experimental atherosclerosis in rabbits. *Atherosclerosis*, 1977, 26:379–386.
80. Bordia A, Verma SK. Effect of garlic on regression of experimental atherosclerosis in rabbits. *Artery*, 1980, 7:428–437.
81. Mohammad SF et al. Isolation, characterization, identification and synthesis of an inhibitor of platelet function from *Allium sativum. Federation proceedings*, 1980, 39:543A.
82. Castro RA et al. Effects of garlic extract and three pure components from it on human platelet aggregation, arachidonate metabolism, release reaction and platelet ultrastructure. *Thrombosis research*, 1983, 32:155–169.
83. Srivastava KC. Aqueous extracts of onion, garlic and ginger inhibit platelet aggregation and alter arachidonic acid metabolism. *Biomedica biochimica acta*, 1984, 43:S335–S346.
84. Makheja AN, Bailey JM. Antiplatelet constituents of garlic and onion. *Agents and actions*, 1990, 29:360–363.
85. Srivastava KC. Effects of aqueous extracts of onion, garlic and ginger on platelet aggregation and metabolism of arachidonic acid in the blood vascular system: in vitro study. *Prostaglandins and leukotrienes in medicine*, 1984, 13:227–235.
86. Srivastava KC, Justesen U. Isolation and effects of some garlic components on platelet aggregation and metabolism of arachidonic acid in human blood platelets. *Wiener Klinische Wochenschrift*, 1989, 101:293–299.
87. Sendl A et al. Comparative pharmacological investigations of *Allium ursinum* and *Allium sativum. Planta medica*, 1992, 58:1–7.
88. Chauhan LS et al. Effect of onion, garlic and clofibrate on coagulation and fibrinolytic activity of blood in cholesterol fed rabbits. *Indian medical journal*, 1982, 76:126–127.
89. Makheja AN, Vanderhoek JY, Bailey JM. Inhibition of platelet aggregation and thromboxane synthesis by onion and garlic. *Lancet*, 1979, i:781.

90. Ariga T, Oshiba S. Effects of the essential oil components of garlic cloves on rabbit platelet aggregation. *Igaku to seibutsugaku*, 1981, 102:169–174.
91. Agarwal KC. Therapeutic actions of garlic constituents. *Medical research reviews*, 1996, 16:111–124.
92. Jain MK, Apitz-Castro R. Garlic: A product of spilled ambrosia. *Current science*, 1993, 65:148–156.
93. Mohammad SM, Woodward SC. Characterization of a potent inhibitor of platelet aggregation and release reaction isolated from *Allium sativum* (garlic). *Thrombosis research*, 1986, 44:793–806.
94. Ariga T, Oshiba S, Tamada T. Platelet aggregation inhibitor in garlic. *Lancet*, 1981, i:150–151.
95. Srivastava KC, Tyagi OD. Effects of a garlic-derived principal (ajoene) on aggregation and arachidonic acid metabolism in human blood platelets. *Prostaglandins, leukotrienes, and essential fatty acids*, 1993, 49:587–595.
96. Jamaluddin MP, Krishnan LK, Thomas A. Ajoene inhibition of platelet aggregation: possible mediation by a hemoprotein. *Biochemical and biophysical research communications*, 1988, 153:479–486.
97. Jain RC, Konar DB. Blood sugar lowering activity of garlic (*Allium sativum* Linn.). *Medikon*, 1977, 6:12–18.
98. Jain RC, Vyas CR, Mahatma OP. Hypoglycaemic action of onion and garlic. *Lancet*, 1973, ii:1491.
99. Jain RC, Vyas CR. Garlic in alloxan-induced diabetic rabbits. *American journal of clinical nutrition*, 1975, 28:684–685.
100. Osman SA. Chemical and biological studies of onion and garlic in an attempt to isolate a hypoglycemic extract. In: *Proceedings of the fourth Asian Symposium of Medicinal Plants and Spices*. Bangkok, 1980:117.
101. Zacharias NT et al. Hypoglycemic and hypolipidemic effects of garlic in sucrose fed rats. *Indian journal of physiology and pharmacology*, 1980, 24:151–154.
102. Srivastana VK, Afao Z. Garlic extract inhibits accumulation of polyols and hydration in diabetic rat lens. *Current science*, 1989, 58:376–377.
103. Farva D et al. Effects of garlic oil on streptozotocin-diabetic rats maintained on normal and high fat diets. *Indian journal of biochemistry and biophysics*, 1986, 23:24–27.
104. Venmadhi S, Devaki T. Studies on some liver enzymes in rats ingesting ethanol and treated with garlic oil. *Medical science research*, 1992, 20:729–731.
105. Kumar CA et al. *Allium sativum*: effect of three weeks feeding in rats. *Indian journal of pharmacology*, 1981, 13:91.
106. Chi MS, Koh ET, Stewart TJ. Effects of garlic on lipid metabolism in rats fed cholesterol or lard. *Journal of nutrition*, 1982, 112:241–248.
107. Swanston-Flatt SK et al. Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice. *Diabetologia*, 1990, 33:462–464.

108. Mathew PT, Augusti KT. Studies on the effects of allicin (diallyl disulfide-oxide) on alloxan diabetes. Part I. Hypoglycemic action and enhancement of serum insulin effect and glycogen synthesis. *Indian journal of biochemistry and biophysics*, 1973, 10:209–221.
109. Mascolo N et al. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytotherapy research*, 1987, 1:28–31.
110. Wagner H, Wierer M, Fessler B. Effects of garlic constituents on arachidonate metabolism. *Planta medica*, 1987, 53:305–306.
111. Gaffen JD, Tavares IA, Bennett A. The effect of garlic extracts on contractions of rat gastric fundus and human platelet aggregation. *Journal of pharmacy and pharmacology*, 1984, 36:272–274.
112. Aqel MB, Gharaibah MN, Salhab AS. Direct relaxant effects of garlic juice on smooth and cardiac muscles. *Journal of ethnopharmacology*, 1991, 33:13–19.
113. Rashid A, Hussain M, Khan HH. Bioassay for prostaglandin-like activity of garlic extract using isolated rat fundus strip and rat colon preparation. *Journal of the Pakistan Medical Association*, 1986, 36:138–141.
114. Neil HA, Silagy CA. Garlic: its cardioprotectant properties. *Current opinions in lipidology*, 1994, 5:6–10.
115. Silagy CA, Neil A. A meta-analysis of the effect of garlic on blood pressure. *Journal of hypertension*, 1994, 12:463–468.
116. Silagy CA, Neil A. Garlic as a lipid lowering agent: a meta-analysis. *Journal of the Royal College of Physicians of London*, 1994, 28:39–45.
117. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. A meta-analysis. *Annals of internal medicine*, 1993, 119:599–605.
118. Brosche T, Platt D. Garlic as a phytogenic lipid lowering drug: a review of clinical trials with standardized garlic powder preparation. *Fortschritte der Medizin*, 1990, 108:703–706.
119. Harenberg J, Giese C, Zimmermann R. Effects of dried garlic on blood coagulation, fibrinolysis, platelet aggregation, and serum cholesterol levels in patients with hyperlipoproteinemia. *Atherosclerosis*, 1988, 74:247–249.
120. Bordia A et al. Effect of essential oil of garlic on serum fibrinolytic activity in patients with coronary artery disease. *Atherosclerosis*, 1977, 26:379–386.
121. Chutani SK, Bordia A. The effect of fried versus raw garlic on fibrinolytic activity in man. *Atherosclerosis*, 1981, 38:417–421.
122. Wolf S, Reim M. Effect of garlic on conjunctival vessels: a randomised, placebo-controlled, double-blind trial. *British journal of clinical practice*, 1990, 44:36–39.
123. Kiesewetter H, Jung F. Beeinflusst Knoblauch die Atherosklerose? *Medizinische Welt*, 1991, 42:21–23.
124. Jung H, Kiesewetter H. Einfluss einer Fettbelastung auf Plasmalipide und kapillare Hautdurchblutung unter Knoblauch. *Medizinische Welt*, 1991, 42:14–17.

125. Bordia A. Klinische Untersuchung zur Wirksamkeit von Knoblauch. *Apotheken-Magazin*, 1986, 6:128–131.
126. Bordia A. Knoblauch und koronare Herzkrankheit: Wirkungen einer dreijährigen Behandlung mit Knoblauchextrakt auf die Reinfarkt- und Mortalitätsrate. *Deutsche Apotheker Zeitung*, 1989, 129:16–17.
127. Sitprija S et al. Garlic and diabetes mellitus phase II clinical trial. *Journal of the Medical Association of Thailand*, 1987, 70:223–227.
128. Burnham BE. Garlic as a possible risk for postoperative bleeding. *Plastic and reconstructive surgery*, 1995, 95:213.
129. Petry JJ. Garlic and postoperative bleeding. *Plastic and reconstructive surgery*, 1995, 96:483–484.
130. Sunter WH. Warfarin and garlic. *Pharmaceutical journal*, 1991, 246:722.
131. Schimmer O et al. An evaluation of 55 commercial plant extracts in the Ames mutagenicity test. *Pharmazie*, 1994, 49:448–451.
132. Zhang YS, Chen XR, Yu YN. Antimutagenic effect of garlic (*Allium sativum*) on 4NQO-induced mutagenesis in *Escherichia coli* WP2. *Mutation research*, 1989, 227:215–219.
133. Siegers CP. *Allium sativum.* In: De Smet PA et al., eds. *Adverse effects of herbal drugs*, *Vol. 1*. Berlin, Springer-Verlag, 1992:73–76.
134. Rose KD et al. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: A case report. *Neurosurgery*, 1990, 26:880–882.

Radix Althaeae*

Definition

Radix Althaeae consists of the dried roots of *Althaea officinalis* L. (Malvaceae) (*1–4*).

Synonym

Malva officinalis L. (*5*).

Selected vernacular names

Altea, altee, althea, bardul khatmi, benefischi, bismalva-hibiscus, blanca malva, bon visclo, bourdon de St Jacques, Eibisch, Eibischwurzel, erva molle, guimauve, Heilwurz, hobbiza, Ibischwurz, khairi, khatmi, korzén prawóslazu, marshmallow, marshmallow root, malvaccioniu, malvavisco, marmolone, molotta, Moorish mallow, orvosiziliz gyökér, racine d'althée, racine de guimauve, Sammetpappel, sauvage, Schleimwurzel, suzmool, sweet weed, white mallow, wymote (*3*, *6–8*).

Geographical distribution

Indigenous to western Asia and Europe, and is naturalized in the United States of America (*9*, *10*). Roots are obtained from commercially cultivated plants that are at least 2 years old and harvested in the autumn (*6*, *10*).

Description

A perennial herb with erect, woody stems, 60–120 cm high. Leaves alternate, ovate to slightly cordate, serrate, velvety, large, occasionally 3-lobed. Flowers pale pink, axillary, the calyx of each surrounded by a 6–9 cleft involucre. Fruit a set of cocci united into a ring (*11*).

Plant material of interest: dried roots

General appearance

Cylindrical or tapering, slightly twisted roots, up to 2 cm thick, with deep longitudinal furrows. Outer surface greyish-brown, bearing numerous

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

rootlet scars. Fracture externally fibrous, internally rugged and granular; section shows a thick, whitish bark with brownish periderm, separated by a well-marked, brownish cambium from the white xylem; stratified structure of the bark and radiate structure of xylem become more distinct when moist. Peeled root has greyish-white finely fibrous outer surface; cork and external cortical parenchyma absent (*2*).

Organoleptic properties

Odour: faint, aromatic; taste: mucilaginous (*1*).

Microscopic characteristics

Phloem with numerous long, thin-walled, non-lignified fibres arranged in tangential groups alternating with groups of sieve tissue, with a ground tissue of thin-walled parenchyma; xylem containing reticulate or scalariform thickening and bordered pits accompanied by lignified tracheids, a small amount of lignified parenchyma and occasional small groups of fibres with only the middle lamella lignified; xylem and phloem transversed by numerous non-lignified medullary rays, mostly uniseriate; majority of parenchyma cells of the phloem and medullary rays contain abundant small starch grains which are mostly simple, spherical to ovoid, occasionally 2–3 compound, with a well-marked circular or slit-shaped hilum; some of these parenchyma cells contain cluster crystals of calcium oxalate 20–40 µm in diameter, while others exist as idioblasts containing mucilage (*1*).

Powdered plant material

Brownish-grey (unpeeled root) or whitish (peeled root). Fragments of colourless, mainly unlignified, thick-walled fibres with pointed or split ends; fragments of reticulate or scalariform thickening and bordered pits; cluster crystals of calcium oxalate about 20–35 µm, mostly 25–30 µm, in diameter; parenchyma cells containing mucilage; fragments of cork with thin-walled, tabular cells in the powdered material from the unpeeled root. Numerous starch grains, 3–25 µm in diameter, with occasionally a longitudinal hilum; starch grains mostly simple, a few being 2–4 compound (*2*).

General identity tests

Macroscopic and microscopic examinations (*1*, *2*).

Purity tests

Microbiology

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter
Not more than 2% of brown, deteriorated drug and not more than 2% of cork in the peeled root (*2*).

Total ash
Not more than 6% in the peeled root and not more than 8% in the unpeeled root (*2*).

Acid-insoluble ash
Not more than 3% in the peeled root (*1*).

Water-soluble extractive
Not less than 22% (*1*).

Loss on drying
Not more than 12% (*2*).

Swelling index
Not less than 10 (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*13*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Not less than 10% total mucilage in the peeled root as determined by gravimetric analysis (*14*).

Major chemical constituents

The mucilage content ranges from 10 to 20% and consists of a mixture of acidic galacturonorhamnans, neutral glucans and neutral arabinogalactans (*6*, *8*, *9*, *15–17*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As a demulcent for symptomatic treatment of dry irritable coughs and irritations of oral and pharyngeal mucosa and as an emollient for wounds and dry skin (*8*, *18–23*). Also used in cough mixtures to mask the bitter or pungent taste of other drugs (*16*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, cystitis, dysentery and irritations of the gastric mucosa (*7*).

Pharmacology

Experimental pharmacology

The demulcent effects of Radix Althaeae are due to its high content of polysaccharide hydrocolloids, which form a protective coating on the oral and pharyngeal mucosa, soothing local irritation and inflammation (*24*).

Anti-inflammatory activity

A polysaccharide fraction (500 µg/ml) isolated from a root extract had anti-complement activity in human serum in vitro (*25*). Aqueous extracts of the roots stimulated phagocytosis, and the release of oxygen radicals and leukotrienes from human neutrophils in vitro (*26*). The aqueous extract also induced the release of cytokines, interleukin-6 and tumour necrosis factor from human monocytes in vitro, thereby exhibiting anti-inflammatory and immunostimulant activity (*26*). Intraperitoneal administration of isolated mucilage polysaccharides to mice (10 mg/kg body weight) induced a 2.2-fold increase in the phagocytic activity of macrophages as measured by the colloidal carbon clearance test (*27*). However, intragastric administration of an 80% ethanol extract of the roots to rats (100 mg/kg body weight) did not inhibit carrageenan-induced footpad oedema (*28*).

Weak inhibition (17%) of mucociliary transport in isolated, ciliated epithelium of the frog oesophagus was demonstrated after treatment of the isolated tissues with 200 µl of an aqueous root macerate (6.4 g/140 ml) (*29*).

Antitussive activity

Intragastric administration of a polysaccharide fraction, isolated from an aqueous root extract, to cats (50 mg/kg body weight) suppressed the intensity and the frequency of coughs induced by mechanical irritation of laryngopharyngeal and tracheobronchial mucosa (*30*). The antitussive activity of this polysaccharide fraction (50 mg/kg body weight) was as effective as Syrupus Althaeae (1.0 g/kg body weight), and more effective than prenoxdiazine (30 mg/kg body weight) (*30*).

Clinical pharmacology

None.

Contraindications

No information available.

Warnings

No information available.

Precautions

Drug interactions

Simultaneous administration of Radix Althaeae may delay the absorption of other drugs (*8*).

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Radix Althaeae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

No information available.

Dosage forms

Peeled or unpeeled, broken, chopped or powdered crude drug (*1*, *2*) and galenical preparations thereof. Store in a well-closed container, protected from light (*2*).

Posology

(Unless otherwise indicated)

For dry cough, oral or pharyngeal irritation: 0.5–3.0 g of crude drug as an aqueous, cold macerate (*14*, *19*, *20*, *31*) or 2–8 ml of syrup (*20*, *22*, *32*), which may be repeated up to a daily dose of 15 g of crude drug. For gastric irritation: 3–5 g of crude drug as an aqueous, cold macerate up to three times daily (*19*, *20*, *31*).

References

1. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
2. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
3. *Farmakopea Polska V, Suplement I.* Warsaw, Polskie Towarzystwo Farmaceutyczne, 1995.
4. *Pharmacopoeia Hungarica*, 7th ed. Budapest, Hungarian Pharmacopoeia Commission, Medicina Konyvkiado, 1986.
5. Hooker JD, Jackson BD. *Index Kewensis. Vol. 1.* Oxford, Clarendon Press, 1895.
6. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
7. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
8. Hänsel R et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Bd. 6: Drogen P-Z*, 5th ed. Berlin, Springer-Verlag, 1994.
9. Leung AY, Foster S. *Encyclopedia of common natural ingredients used in food, drugs, and cosmetics*, 2nd ed. New York, NY, John Wiley & Sons, 1996.
10. Leung AY. *Encyclopedia of common natural ingredients*. New York, NY, John Wiley & Sons, 1980.
11. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, PA, Blakiston, 1950.
12. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
13. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
14. *Pharmacopée française*. Paris, Adrapharm, 1996.

15. Blaschek W, Franz G. A convenient method for the quantitative determination of mucilage polysaccharides in Althaeae radix. *Planta Medica*, 1986, 52:537.
16. Samuelsson G, ed. *Drugs of natural origin, a textbook of pharmacognosy*. Stockholm, Swedish Pharmaceutical Press, 1992.
17. Tomoda M et al. The structural features of *Althaea*-mucilage representative mucous polysaccharide from the roots of *Althaea officinalis. Chemical and Pharmaceutical Bulletin*, 1980, 28:824–830.
18. Bone K. Marshmallow soothes cough. *British Journal of Phytotherapy*, 1993/1994, 3:93.
19. Marshmallow root. In: Bradley PR, ed. *British herbal compendium. Vol. 1.* Bournemouth, British Herbal Medicine Association, 1992:151–153.
20. *ESCOP monographs on the medicinal uses of plant drugs.* Fascicule 1. Elberg, European Scientific Cooperative on Phytotherapy, 1996.
21. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
22. Reynolds JEF, ed. *Martindale, the extra pharmacopoeia*, 29th ed. London, Pharmaceutical Press, 1989.
23. Weiss RF. *Lehrbuch der Phytotherapie*, 7th ed. Stuttgart, Hippokrates Verlag, 1991.
24. Franz G. Polysaccharides in pharmacy: current applications and future concepts. *Planta Medica*, 1989, 55:493–497.
25. Yamada H et al. Relationship between chemical structure and anti-complementary activity of plant polysaccharides. *Carbohydrate Research*, 1985, 144:101–111.
26. Scheffer J et al. Radix althaeae und Flores chamomillae Extrakte auf Entzündungsreaktionen humaner neutrophiler Granulozyten, Monozyten und Rattenmastzellen. In: *Abstracts of the Third Phytotherapy Congress.* Lübeck-Travemünde, 1991: Abstract P9.
27. Wagner H, Proksch A. Immunostimulatory drugs of fungi and higher plants. In: Wagner H, Hikino H, Farnsworth NR, eds. *Economic and medicinal plant research. Vol. 1.* Orlando, FL, Academic Press, 1985:111–153.
28. Mascolo N et al. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytotherapy Research*, 1987, 1:28–31.
29. Müller-Limmroth W, Fröhlich HH. Wirkungsnachweis einiger phytotherapeutischer Expektorantien auf den mukoziliaren Transport. *Fortschritte der Medizin*, 1980, 98:95–101.
30. Nosal'ova G et al. Antitussive efficacy of the complex extract and the polysaccharide of marshmallow (*Althaea officinalis* L. var. *Robusta*). *Pharmazie*, 1992, 47:224–226.
31. Wichtl M. Eibischwurzel. In: Wichtl M, ed. *Teedrogen*, 2nd ed. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1989:146–147.
32. *British pharmaceutical codex*. London, Pharmaceutical Press, 1934.

Herba Bidentis

Definition

Herba Bidentis consists of the whole or cut dried aerial parts of *Bidens tripartita* L. (Asteraceae), collected at the time of mass budding, which marks the onset of the flowering phase (*1*).

Synonyms

Bidens acuta (Wiegand) Britton, *B. comosa* (Gray.) Wieg., *B. connata* Muhl. ex Willd., *B. hirta* Jordan in Gren. & Godr., *B. nodiflora* L., *B. nodiflora* Lév. & Vaniot, *B. shimadai* Hayata, *B. taquetii* Lev. & Van., *B. tripartia* L., *Hepatorium* sp. (*2–4*).

Selected vernacular names

Bastard agrimony, bastard hemp, beggar-ticks, bident á feuilles tripartites, bident trifolié, bident tripartite, brønnsle, bur beggarsticks, bur marigold, càñamo acuàtico, cârligior, chamguisari, dentită, dokaebibaneul, Dreiteiliger Zweizahn, forbicina comune, gatalryukcho, guichimchae, guichimcho, guiwoocho, kolmisruse, langyecae, lang ba cao, lang pa ts'ao, longbacao, orkbila, paneuldaksari, papachim, purple-stem beggarticks, purplestem beggarticks, qinnab maiy, railway beggar's tick, spanish needles, sticktights, strzalki, sunītis nokarenais, sunītis trejdaivu, sukeneviri, swamp beggar-ticks, ta-ukogi, tel maiy, three-lobe beggarticks, threelobe beggarticks, thsereda trjohrazdelnaja, trifid bur-marigold, tripartite bur marigold, tuldokaebibaneul, tummarusokki, uczep dwuzebny, uczep trojdzielny, veerdelig tandzaad, water agrimony, water hemp, wolf's grasp weed (*2*, 3–*14*).

Geographical distribution

Indigenous to damp and temperate regions near fresh water sources throughout Asia, Africa, Australia, Europe, North America and New Zealand. The plant is found in the damp regions of the Newly Independent States, such as in Northern Siberia and the southern part of the far east region (*4*, *5*, *15–17*).

Description

An annual plant, 15–75(100) cm high, fibrous root, adventitious roots when growing in wetlands. Stem erect, heavily branched, wiry, angular, solid, marked with small brown spots, glabrous or somewhat downy, often brownish-red. Leaves opposite, simple (but appearing trifoliate), 3- to 5-lobed (usually deeply divided into 3 narrow ovate-rhomboid to lanceolate lobes, the central one larger and wider), sharply serrate, acuminate, 3–15 cm long, dark green, petiole narrow, short and winged. Uppermost leaves sometimes undivided. Inflorescence: flower head (50–60 flowers), generally discoid, erect or inclined, solitary or not, conical, 15–25 mm long and 15–25 mm wide. Peduncle 1–6 cm long. Involucre 7–20 mm in diameter, two rows of phyllaries: inner phyllaries ovate, 6–8 mm long, brown-yellow; outer phyllaries, usually 5–8, lanceolate, leaf shaped with thorny edges, green. Bracts linear, spreading, ray flowers absent, disc flowers hermaphrodite, tubular, brownish-yellow. Fruit, glabrous achene, wedge-shaped, distinctly compressed; inner achenes 5–8 mm long, 4-angled; outer achenes 3.5–4 mm long, 2–3-angled; thorns of angles ascending below, reflexed above; pappus awns thorny, generally 2, sometimes 3–4 (2 longer), 1–3.6 mm (*4–6*, *9*, *15*, *16*, *18–22*).

Plant material of interest: dried aerial parts

General appearance

Entire or fragmented leafy stems, leaves and flower heads. Leaves opposite, short petiolate, 3–5-lobed or undivided, 3–7 cm in length (no longer than 15 cm), dark green. Leaf fragments crumpled, the serrated edges can be distinguished. Stems heavily branched, glabrous or somewhat downy, not more than 0.8 cm in thickness, green or greenish-violet. Stem pieces hollow or pithy, wrinkled. Flower heads, not more than 0.6–1.5 cm in diameter, somewhat drooping. Disc flowers tubular, with two awns, brownish-yellow (*1*, *5*, *6*, *16*, *23*).

Organoleptic properties

Odour: slight; taste: bitter and slightly astringent (*1*).

Microscopic characteristics

Leaf: upper and lower epidermises with undulating cell walls are distinguishable. Anomocytic stomata. Simple hairs with thin cell walls on both epidermises, 9–18 cells, sometimes filled with brown contents; very large base cell with a longitudinally striated cuticle. Simple hairs with thick cell walls on the veins and at the edges of the leaf, 2–13 cells; the hair base

multicellular with a longitudinally striated cuticle. Secretion ducts filled with dark red liquid, along veins and near the leaf edges. Flower: florets with two opposing barbed, blunt-ended pappus spines from the top of the ovary, and as long as the tubular corolla, consisting of a multicellular column of cells about 200 µm in diameter including some vascular tissue, with many thorn-like unicellular covering trichomes about 350 µm long directed towards the pappus base. Pollen grains spherical, with a spiny exine and three pores, about 30 µm in diameter (*1*, *23*).

Powdered plant material

Green, brown-green or green-violet with a sprinkling of yellow. The powder has the same microscopic characteristics as the entire leaf and flower (see Microscopic characteristics) (*1*).

General identity tests

Macroscopic and microscopic examinations; thin-layer chromatography, paper chromatography and chromatography–mass-spectroscopy for the presence of flavonoids (*1*, *24*); chemical tests for the presence of polysaccharides (precipitation with ethanol and reduction of simple sugars results after the acid hydrolysis of polysaccharides) (*1*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*25*).

Chemical

The paper chromatogram (chromatography paper FN 12, Germany; n-butanol-acetic acid-water (4:1:2); 16 hours; ultraviolet (UV) light, 360 nm) shows two dark brown zones of flavonoids with Rf values of about 0.38 and 0.58. A dark-brown zone with an Rf value of about 0.75 should not be present since it indicates the presence of flavonoids of *Bidens cernua* L.) (*1*).

Foreign organic matter

Not more than 40% stems or their fragments; not more than 8% of parts with non-characteristic colour of the plant material; not more than 3% of other foreign organic matter (fragments of non-toxic plants). For cut drug: not more than 10% of fragments having a diameter more than

7 mm; not more than 15% of fragments having a diameter less than 0.5 mm (*1*).

Total ash
Not more than 14% (*1*).

Acid-insoluble ash
No information available.

Sulfated ash
No information available.

Water-soluble extractive
No information available.

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 13% (*1*).

Swelling index
Not applicable.

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg. For other pesticides, see the *European pharmacopoeia* (*24*), WHO guidelines on quality control methods for medicinal plants (*25*) and WHO guidelines on pesticide residues (*26*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*25*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*25*) for the analysis of radioactive isotopes.

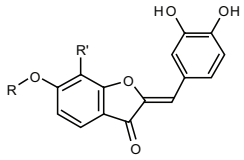
Other purity tests
Acid-insoluble, sulfated ash, water-soluble extractive and alcohol extractive tests to be established in accordance with national requirements. Content of mineral matter not more than 1% (*1*).

Chemical assays

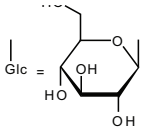
Contains not less than 3.5% polysaccharides, determined by chemical assays (*1*).

Major chemical constituents

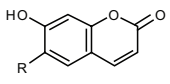
The major constituents of the dried aerial parts are flavonoids (luteolin, cynaroside), related chalcones (butein, butein-7-*O*-β–d-glucopyranoside and marein), flavanones (isocoreopsin and flavanomarein) and aurones (sulfuretin, sulfurein, maritimetin and maritimein) (*5*, *16*, *27*, *29*, *30*). Dried aerial parts contain 0.05–0.11% (v/w) essential oil and 4.51–4.65% saccharides (arabinose, galactose, glucose, rhamnose and xylose) (*31*, *32*). The presence of coumarins (umbelliferone, scopoletin and aesculetin), tridecane-derived polyacetylenes (for example trideca-1,12-dien-3,5,7,9-tetrayne), tannins, xanthophyll (a yellow pigment, widespread in nature, sometimes called lutein), organic acids, carotene and vitamin C has also been reported (*5*, *16*, *27–30*, *33*, *34*). The structures of the major constituents are presented below.



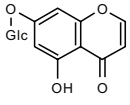
maritimetin R = H R' = OH
maritimein R = Glc R' = OH
sulfuretin R = H R' = H
sulfurein R = Glc R' = H



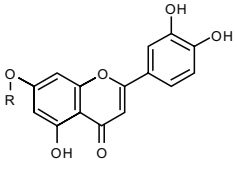
β-d-glucopyranosyl



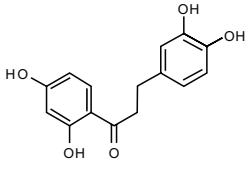
umbelliferone R = H
aesculetin R = OH
scopoletin R = OCH_3



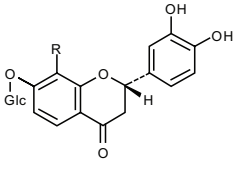
cynarozid



luteolin R = H
cynarozide R = Glc



butein



isocoreopsin R = H
flavanomarein R = OH

Medicinal uses

Uses supported by clinical data

Internally used for treatment of chronic dysentery, and acute and chronic enteritis (*35*). Oral administration and simultaneous external application have been used in patients with psoriasis (*17*).

Uses described in pharmacopoeias and well-established documents

Internally: as a mild sudorific and diuretic for treatment of bladder and kidney problems, for conditions producing blood in the urine (haematuria) (*36*), as an astringent, and for treatment of diarrhoea and ulcerative colitis (*15*, *28*).

Uses described in traditional medicine

As a diuretic, antidiarrhoeal, antiallergic, anti-inflammatory (*37*), anthelminthic, febrifuge, diaphoretic, for gallbladder and as a kidney tonic (*38*). Used for the treatment of alopecia (*4*), scrofulosis (*39*), gout, arthralgia (*40*), furunculosis, diathesis (a constitutional predisposition towards a particular state or condition and especially one that is abnormal or diseased), seborrhoeic dermatitis, acne vulgaris (*17*, *27*, *41–43*), eczema (*44*), infantile rickets (*45*, *46*), digestive tract ailments, flatulence, fevers, bladder and kidney stones, as a styptic haemostatic and for curing insect bites (*47*). Used externally as a bath for various diathesis conditions, especially in children (*28*).

Pharmacology

Experimental pharmacology

Antimalarial activity

A 90% ethanol extract of the dried whole plant was active against *Plasmodium falciparum* at a concentration of 20 µg/ml (*48*).

Choleretic activity

Oral administration of the total flavonoids isolated from the aerial parts of the plant to rats (500 mg/kg body weight (bw)) significantly induced choleretic activity. Subsequently, an increase of cholic acids and cholesterol in bile was observed (*49*).

Antiulcer activity

Separate intragastric administration of methanol and aqueous extracts of the aerial parts to rats, at a dose of 500 mg/kg bw, showed antiulcer activ-

ity in vivo against aspirin-induced ulcers, but the extracts were inactive against indomethacin-induced ulcers (*50*).

Photoprotective activity

Haemolysis induced in vitro by psoralen and UV-A radiation (PUVA-haemolysis) was inhibited by the presence of an extract of the aerial parts of the plant in the medium during irradiation, or by the addition of the extract to the medium after PUVA-treatment. The inhibition effect was more pronounced when the extract was added during irradiation (*51*).

Toxicology

An ethanol-aqueous extract (1:1) of the aerial parts administered intraperitoneally to mice had a median lethal dose of 750 mg/kg bw (*52*).

Clinical pharmacology

Aerial parts of the plant were used in an open clinical trial, without a control group, to treat 500 patients with dysentery, 65 with acute enteritis and 248 with chronic enteritis. Several different dosage forms of the herb were used: 200 g of fresh whole herb and 100 g of dried herb in decoctions (in three divided doses per day); granules containing 5 g of dried aqueous extract, three times daily; 0.5 g tablets of dried aqueous extract, 10 tablets each time, three times daily; and injection, 2 ml per injection (dose not stated), 2–3 times daily. The herbal preparations were administered for 3–10 days to patients who had already had diarrhoea for 7–15 days. Of the 500 patients with chronic dysentery, 387 were reported to have been cured; 13 had not responded within 3 days. All 313 patients with enteritis were reported to have been cured (12 of the patients with chronic enteritis relapsed later) (*35*).

In an open clinical trial without a control group, a 70% ethanol extract of the aerial parts of the plant and an ointment containing 2.5% of the extract were administered to 53 patients with psoriasis. After oral administration of the extract (20 drops three times daily) and simultaneous application of the ointment to the affected areas of the skin once a day, the combination was found to have anti-inflammatory activity as well as an ability to stimulate adrenal functions. After one week of treatment, desquamation of the skin was decreased, and a decoloration of the psoriatic plaques was observed. A clinical recovery was recorded for 29 of the patients; an improvement in condition was recorded for 22 patients; and a failure of treatment for 2 patients (*17*).

Adverse reactions
No information was found.

Contraindications
No irrigation therapy is recommended in people with oedema due to impaired heart or kidney function. If signs of hypersensitivity reactions appear, Herba Bidentis must not be used again.

Warnings
No information was found.

Precautions

Drug interactions
No information was found.

Other precautions
No information was found.

Pregnancy
Preparations of Herba Bidentis should not be used during pregnancy.

Nursing mothers
Preparations of Herba Bidentis should not be used by nursing mothers.

Paediatric use
Preparations of Herba Bidentis should not be used for the treatment of children under the age of 12 years.

Dosage forms
A herbal tea or a briquette of Herba Bidentis (*17*).

Posology
(Unless otherwise indicated)
Internal use. One tablespoon of the infusion (1:20) is administered 3–4 times a day (*46*, *53*).
External use as a bath. One glass of an infusion of 10 g of cut herb together with 100 g of cooking salt or sea salt per bath (*54*).

References

1. *USSR pharmacopoeia*, 11th ed. Vol. 2. Moscow, Meditsina, 1990 [in Russian].
2. *Plants for a future. Database* (http://www.ibiblio.org/pfaf/database/latinB.html).
3. Schroeter AL, Panasiuk VA. *Dictionary of plants names*. Koenigstein, Koeltz Scientific Books, 1999.
4. Bown D. *Encyclopedia of herbs and their uses*. London, Dorling Kindersley, 1995.
5. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific, 2000.
6. Grieve M, Leyel CF, eds. *A modern herbal.* London, Tiger Books International, 1998.
7. Yakoblev GP, Blinova KF eds. *Entsiklopeditsheskii slovar' lekarstvenn'h rasteni i produktov zhivotnogo proishohzhdenija*. St Petersburg, SpetzLit, 1999.
8. *Lexique des plantes médicinales. Version 2.01.* Montreal, PASSEPORT-SANTE.NET (http://www.passeportsante.net/fr/Solutions/DocumentsReference/Lexique.aspx).
9. Parvu C. *Enciclopedia plantelor*. Vol. II. Bucharest, Editura Tehnica, 2003.
10. Ohwi J. *Compositae flora of Japan*. Washington, DC, Smithsonian Institution, 1965.
11. Makaschvili A. *Lexicon botanicum. Nomina plantarum.* Tbilisi, Metsiniereba, 1991.
12. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
13. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
14. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
15. Chevallier A. *The encyclopedia of medicinal plants*. London, Dorling Kindersley, 1996.
16. Yakovlev GP, Blinova KF, ed. *Lekarstvennoje, elnoje syr'jo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
17. Sokolov SJ, Zamotaev IP**.** *Spravocznik po lekarstvennym rastenijam*. Moscow, Meditsina, 1990.
18. Komarov VL, Shishkin BK. *Flora SSSR. Vol. 25. Pod red.* Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1959.
19. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR. Izd.* Moscow, Mysli, 1976.
20. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR. 3-ie izd*. Kishinev, Shtiintsa, 1986.
21. Alexeev YE et al. *Travianistye rastenia SSSR. Vol. 2*. Moscow, Izdatel'stvo Mysl', 1971.

22. Kuznetsova MA, P'batshuk IZ. *Farmakognozija*. Moscow, Meditsina, 1984.
23. *British herbal pharmacopoeia*. Bournemouth, British Herbal Medicine Association, 1983.
24. *European pharmacopoeia*. 5th ed. Strasbourg, Council of Europe, 2005.
25. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
26. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
27. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Vysshaja shkola, 1983.
28. Muravjova DA. *Farmakognozija.* Moscow, Meditsina, 1991.
29. Muravjova DA, Samylina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
30. Baranska K. Certain flavonoids occurring in Bidens tripartitus. *Acta Poloniae Pharmaceutica*, 1963, 5:357–364.
31. Ivanic R, Miric M, Lukis P. Examination of chemical constituents of *Bidens tripartitus*. *Acta Pharmacologica Jugoslavia*, 1976, 3:253–256.
32. Karr'jev MO et al. *Soderzanija biologitsheski aktivnõje sojedinenije v rastenijakh flory Turkmeni. Izvestija AN Turkmeskoi SSR. Serija Biologitcheskie Nauki,* 1981, 4:54–66.
33. Wren RC. *Potter's new cyclopaedia of botanical drugs and preparations.* Essex, CW Daniel, 1975.
34. *Rastitel'nye resursy SSSR*. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. *Vol. 7*. Leningrad, Nauka, 1993.
35. Zhang Shoutai. Treatment of 500 cases of dysentery with *Bidens tripartita. Shandong Journal of Traditional Chinese Medicine*, 1989, 8:11–12.
36. Wren RC. *Potter's new cyclopedia of botanical drugs and preparations.* Saffron Walden, CW Daniel, 1988.
37. Zadorozhnyi AM et al. *Spravotchnik po lekarstvennim rastenijam*. Moscow, Lesnaja promyshlennost', 1988.
38. Yakovlev GP, Blinova KF, ed. *Rastenija dlja nas.* St Petersburg, Utchebnaja kniga, 1996.
39. Grodzinskii AM, ed. *Lekarski roslini. Entsiklopedicznyi dovidnik.* Kiiv, Redaktsija Ukrainskoi entsiklopedii, 1991.
40. Bazaron EG, Aseeva TA, eds. *Vaidurya-Onbo*, *Tractat indotibetskoi meditsiny.* Novosibirsk, Vaidurya-Onbo, 1984.
41. Lager AA. *Fitoterapija.* Krasnojarsk, Izdatel'stvo krasnojarskogo universiteta, 1988.

42. Kortikov VN, Kortikov AV. *Polnyi spravotchnik lekarstvennykh rasteni* [*The complete reference of medicinal plants*]. Rostov-na-Donu, Fenix, 2002.
43. Sezik E et al. Folk medicine in Uzbekistan I. Tashkent, Djizzax, and Samarqand provinces. *Journal of Ethnopharmacology*, 2004, 92:197–207.
44. Duke JA, Ayensu ES. *Medicinal plants of China*. Algonac, MI, Reference Publications, 1985.
45. Kukes VG, ed. *Fitoterapija s osnovami klinitcheskoj farmakologii*. Moscow, Meditsina, 1999.
46. Ladynina EA, Morozova RS. *Fitoterapija*. Leningrad, Meditsina, 1987.
47. Zargari A. *Medicinal plants. Vol. 3*. Tehran, Tehran University Publications, 1992.
48. Brandao MG et al. Antimalarial activity of extracts and fractions from *Bidens pilosa* and other Bidens species (Asteraceae) correlated with the presence of acetylene and flavonoid compound. *European Journal of Pharmacology*, 1997, 57:131–138.
49. Kovaleva NG. *Letchenie rastenijami (Otcherki fitoterapii)*. Moscow, Meditsina, 1971.
50. Muto Y et al. Studies on antiulcer agents. I. The effects of various methanol and aqueous extracts of crude drugs on antiulcer activity. *Yakugaku Zasshi*, 1994, 114:980–994.
51. Bezdetnaya LN. Inhibition of psoralen photosensitized hemolysis by *Bidentis tripartita* extract. *Biofizika*, 1992, 37:91–93.
52. Bhakuni DS et al. Screening of Indian plants for biological activity. Part III. *Indian Journal of Experimental Biology*, 1971, 9:91.
53. Stoianov N. *Nashije lekarstveni rastenija. I* [*Our medicinal herbs*]. Sofija, Izd. Nauka i izkustva, 1972.
54. Turova AD. *Lekarstvennye rastenija SSSR i ikh primenenie*. Moscow, Meditsina, 1974.

Flos Calendulae*

Definition
Flos Calendulae consists of the dried ligulate florets or composite flowers of *Calendula officinalis* L. (Asteraceae) (*1–3*).

Synonyms
Asteraceae are also known as Compositae.

Selected vernacular names
Atunjaq, calendula, Chinese safflower, cuc kim tiên, djamir, djomaira, feminell, flamenquilla, fleur de calandule, fleur de souci, fleur de souci officinal, fleurs de tous les mois, garden marigold, gold-bloom, Goldblume, gole hamisheh bahar, hen and chickens, Körömvirag, lellousha, maravilla, marigold, mary-bud, ok-hhawan, pot marigold, qaraqus, qawqhan, quaqahan, ringflower, Ringelblüten, saialill, sciure'e Sant'antonio, souci, souci des jardins, tabsoult, toukinsenka, tousslat, uchu k'aspa, virreina, xu xi, zergul zerzira, zobeida, zubaydah (*4–7*).

Geographical distribution
Indigenous to central, eastern and southern Europe. Cultivated commercially in North America, the Balkans, Eastern Europe and Germany (*6*, *8*).

Description
An annual herb, much branched from the base, very aromatic, up to 0.3–0.6 m high; stem angular, hairy and solid. Leaves sessile, light green, with semiamplexicaul base; entire, undulate or remotely denticulate; glandular hairs on both surfaces; lower leaves spatulate, obtuse, sometimes acute at the apex, 10–20 cm long and 1–4 cm wide; higher leaves oblong and mucronate, 4–7 cm long. Involucral bracts 7–15 mm long, covered with long, glandular hairs; inner involucral bracts with pellucid, scarious margin; marginal flowers in cultivated plants often multi-seriate; corolla oblong-spatulate, bright yellow or orange, 15–25 mm long and 3 mm wide,

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

1–3-toothed with 4 or 5 veins, marginally entire, covered at the base with patent, long, thick hairs; corolla of disc flowers rounded, 3-dentate top, 1.5–2.5 cm long and 4–7 mm in diameter, 5 mm long tube and moderately widened limb. Stigma short, thick, hairy; ovary oblong, 0.5 mm in length, pubescent, shrivelling after anthesis. Achenes narrowly oblong, strongly curved, faintly ribbed, thinly pubescent or glabrous, 10–12 mm long, outer achenes warty-ribbed outside, inner achenes prickly-warty, often with broad, thick margins (*2*, *7*, *9*).

Plant material of interest: dried ligulate florets and composite flowers

General appearance

Ligulate florets consist of a yellow, orange or orange-yellow ligule, 3–5 mm wide and about 7 mm in the middle part, with 3-toothed apex and hairy, partly sickle-shaped, yellowish-brown to orange-brown tube with projecting style and 2-lobed stigma; occasionally with a partly bent yellowish-brown to orange-brown ovary. Tubular florets about 5 mm long, consist of yellow, orange-red or red-violet 5-lobed corolla and yellowish-brown or orange-brown tube, hairy in its lower part, mostly with a bent yellowish-brown to orange-brown ovary (*1*).

Organoleptic properties

Odour: faint, pleasantly aromatic (*10*, *11*); taste: bitter (*2*).

Microscopic characteristics

Inner epidermal cells of ray floret elongated, rectangular and almost straight walled, cuticle faintly striated; stomata absent; outer epidermal cells similar, but with 3 or 4 anomocytic stomata; trichomes very numerous on the tube, biseriate; stigma epidermal cells straight-walled, polygonal. In disc floret, outer epidermal cells elongated, straight or slightly sinuous-walled, stomata absent; abundant trichomes on area below point of insertion of the stamens, mainly glandular, uniseriate or biseriate. Within the upper part of the anthers, a layer of isodiametric to elongated, moderately thick-walled, lignified and pitted cells; pollen grains spherical, up to 45 µm in diameter, with 3 germinal pores, exine finely granular with numerous short spines; apex of stigma covered by short, bulbous papillae (*2*).

Powdered plant material

Yellow-green; fragments of corollas containing light yellow oil droplets; some corollas with fairly large anomocytic stomata, others containing

prismatic and very small clusters of calcium oxalate crystals. Covering trichomes biseriate, multicellular and conical; glandular trichomes with a uniseriate or biseriate, multicellular stalk and a large, ovoid, biseriate, multicellular head. Spherical pollen grains up to 45 µm in diameter, exine finely granular with numerous short spines and with 3 germinal pores; occasional fragments of stigmas with short, bulbous papillae (*1*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for flavonoid content (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter

Not more than 5% bracts and not more than 2% other foreign matter (*1*, *2*).

Total ash

Not more than 10% (*1*, *2*).

Acid-insoluble ash

Not more than 2% (*2*).

Water-soluble extractive

Not less than 20% (*2*).

Loss on drying

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests

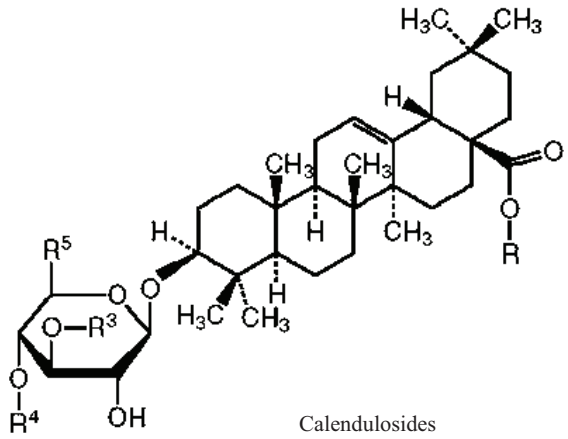
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 0.4% flavonoids, calculated as hyperoside, by spectrophotometry (*1*). A high-performance liquid chromatography method is also available (*15*).

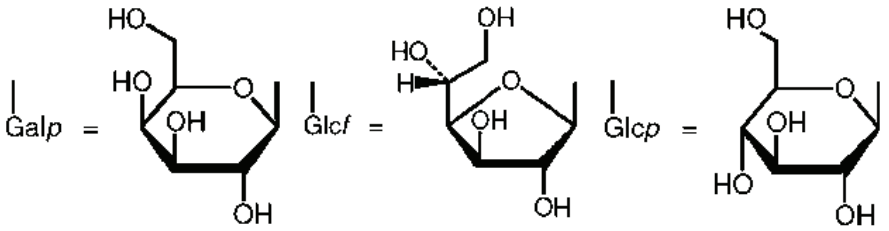
Major chemical constituents

The major constituents are triterpene saponins (2–10%) based on oleanolic acid (i.e. calendulosides) and flavonoids (3-*O*-glycosides of isorhamnetin and quercetin), including astragalin, hyperoside, isoquercitrin and rutin. Other constituents include essential oil, sesquiterpenes (e.g. caryophyllene) and triterpenes (e.g. α- and β-amyrins, lupeol and lupenone) (*5*, *6*, *16*). Polysaccharides have also been reported (*17*). The structures of the characteristic triterpene saponins and flavonoids are presented below.

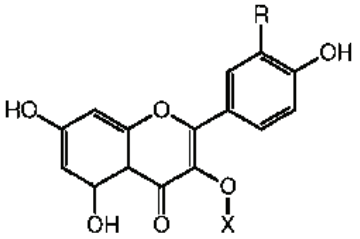


Calendulosides

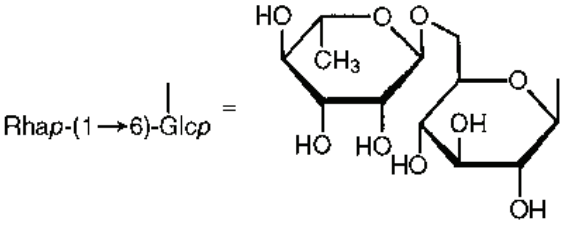
	R	R^3	R^4	R^5
A	H	H	Gal*p*	CH_2OH
E	H	H	H	CO_2H
F	Glc*p*	H	H	CO_2H
H	Glc*p*	Gal*p*	H	CO_2H



β-D-galactopyranosyl β-D-glucofuranosyl β-D-glucopyranosyl



	R	X
astragalin	H	Glc*p*
hyperoside	OH	Gal*p*
isoquercitrin	OH	Glc*f*
rutin	OH	Rha*p*-(1→6)-Glc*p*



O-6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

External treatment of superficial cuts, minor inflammations of the skin and oral mucosa, wounds and ulcus cruris (*2*, *18*, *19*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of amenorrhoea, angina, fevers, gastritis, hypotension, jaundice, rheumatism and vomiting (*2*, *5*, *6*).

Pharmacology

Experimental pharmacology

Phagocytosis

Three polysaccharides isolated from an aqueous extract of Flos Calendulae enhanced phagocytosis in human granulocytes in vitro in the colloidal carbon clearance test (*17*). Intraperitoneal injection of a polysaccharide fraction isolated from an aqueous extract of the flowers to mice (10 mg/kg body weight) enhanced phagocytosis (*20*). Intraperitoneal administration of an unsaponifiable fraction (0.5 ml) of a hydroalcoholic extract of the flowers weakly stimulated phagocytosis in mice inoculated with *Escherichia coli*. However, the hydroalcoholic extract was not active (*21*).

Antimicrobial activity

The essential oil of the flowers inhibited the growth in vitro of *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* (*22*). A flavonoid fraction isolated from the flowers inhibited the growth in vitro of *S. aureus*, *Sarcina lutea*, *E. coli*, *Klebsiella pneumoniae* and *Candida monosa* (*23*). However, chloroform, ethanol, methanol or water extracts of the flowers did not inhibit bacterial growth in vitro (*24–26*). Acetone, ethanol or water extracts inhibited the growth in vitro of the fungus *Neurospora crassa* (*27*). Extracts of the flowers inhibited the growth in vitro of *Trichomonas vaginalis* (*28*). Oxygenated terpenes appear to be responsible for the antimicrobial activity (*29*).

Antiviral activity

A tincture of the flowers suppressed the replication of herpes simplex, influenza A2 and influenza APR-8 viruses in vitro (*30*). However, an aqueous extract of the flowers was not active (*31*). A chloroform extract of the flowers inhibited the replication of HIV-1 in acutely infected lymphocytic MOLT-4 cells in vitro (IC_{50} 0.4 mg/ml) (*32*). A chloroform extract also inhibited HIV-1 reverse transcriptase activity in a dose-dependent manner (ED_{50} 51.0 µg/ml) (*32*). A 5% hot aqueous extract of the

flowers (2 ml) inhibited the replication of encephalitis virus after intraperitoneal administration to mice (*33*).

Anti-inflammatory activity

Topical application of a 70% ethanol extract of the flowers to mice at a dose of 1.2 mg/ear (corresponding to 4.16 mg crude drug) reduced croton oil-induced ear oedema by 20% (*34*). External application of a carbon dioxide extract of the flowers (300 µg/cm^2) suppressed croton oil-induced ear oedema in mice (*34*). The triterpene fraction of an extract of the flowers had marked antiinflammatory activity in mice (1 µg/ear) against ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate (*35*). Faradiol esters isolated from the flowers (240 µg/cm^2) inhibited croton oil-induced ear oedema in mice (*36*). Intragastric administration of an aqueous extract of the flowers (100 mg/kg body weight) inhibited carrageenan-induced footpad oedema in rats (*37*). However, an 80% ethanol extract of the flowers was weakly active (11% inhibition) at a concentration of 100 mg/kg body weight administered orally 1 hour prior to induction of oedema (*38*). Isorhamnetin glycosides isolated from the flowers inhibited rat lung lipoxygenase in vitro (*39*).

Wound-healing activity

External application of a hydroalcoholic extract accelerated the rate of contraction and epithelialization of excision wounds in rats (*40*). A 3% freeze-dried aqueous extract of the flowers induced vascularization in the chick chorioallantoic membrane assay. Histological sections of the treated chorioallantoic membranes also indicated the presence of hyaluronan, a tissue glycosaminoglycan associated with neovascularization (*41*).

Clinical pharmacology

Although no randomized, controlled clinical trials have been performed, two case reports in the early medical literature support the traditional use of Flos Calendulae. The reports describe the use of a strong tincture of the flowers applied on compresses to reduce inflammation and suppuration, and to accelerate the healing of wounds (*42*, *43*). These reports may be of historical value only.

Contraindications

Flos Calendulae is contraindicated in cases of known allergy to plants of the Asteraceae (Compositae) family (*18*).

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Saponins isolated from Flos Calendulae were not mutagenic at a concentration of 400 µg/ml in the *Salmonella*/microsome assay using *S. typhimurium* strain TA98, with or without S9 metabolic activation (*44*). Extracts of the flowers were not carcinogenic after daily intragastric administration of 0.15 g/kg body weight to rats (for 22 months) or hamsters (for 18 months) (*45*). Mutagenicity testing of the fluidextract in the *Salmonella*/microsome assay (using *S. typhimurium* strains TA98, TA100, TA1535 and TA1537) was negative at concentrations of up to 5 mg/plate. The mouse bone marrow micronucleus test was also negative after daily administration of up to 1 g/kg body weight for 2 days (*46*). A fluidextract of the flowers (100 mg/ml, 60% ethanol) was genotoxic in both mitotic crossing-over and chromosome segregation when assayed for mitotic segregation in the heterozygous diploid D-30 of *Aspergillus nidulans* (*46*).

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and nonteratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Calendulae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Weak skin-sensitization has been reported (*47*).

Dosage forms

Infusion for topical use; aqueous and alcohol extracts, tinctures and ointment for external use (*2*, *18*, *19*). Store in a well-closed container, protected from light (*1*).

Posology

(Unless otherwise indicated)

Topical application: an infusion of 1–2 g/150 ml (*18*). External use: a 40% alcohol extract (1:1), or tincture (1:5) in 90% alcohol (*2*). For the treatment of wounds, the tincture is applied undiluted; for compresses, the tincture is usually diluted at least 1:3 with sterile water (*18*, *48*, *49*). Ointment: 2–5% (*48*, *50*).

References

1. *European pharmacopoeia*, 3rd ed., Suppl. 2000. Strasbourg, Council of Europe, 1999.
2. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
3. *Pharmacopoeia Hungarica*, 7th ed. Budapest, Hungarian Pharmacopoeia Commission, Medicina Konyvkiado, 1986.
4. Boulos L. *Medicinal plants of North Africa*. Cairo, Reference Publications, 1983.
5. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL, January 28, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
6. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
7. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, PA, Blakiston, 1950.
8. Leung AY, Foster S. *Encyclopedia of common natural ingredients used in food, drugs, and cosmetics*, 2nd ed. New York, NY, John Wiley & Sons, 1996.
9. Backer CA, Van den Brink B. *Flora of Java. Vol. 2*. Noordfog-Groningen, NVP, 1965: 574.
10. *Pharmacopoea helvetica*, 8th ed. Berne, Département fédéral de l'intérieur, 1997.
11. *Pharmacopée française*. Paris, Adrapharm, 1996.
12. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
13. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
14. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
15. Vidal-Ollivier E et al. Dosage par CLHP. Des flavonoides majoritaires de *Calendula officinalis* L. En fonction de la variété culturale et de la date de récolte. *Pharmaceutica Acta Helvetiae*, 1991, 66:318–320.
16. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
17. Varljen J, Lipták A, Wagner H. Structural analysis of a rhamnoarabinogalactan and arabinogalactans with immunostimulating activity from *Calendula officinalis*. *Phytochemistry*, 1989, 28:2379–2383.
18. *ESCOP monographs on the medicinal uses of plant drugs.* Fascicule 1. Elburg, European Scientific Cooperative on Phytotherapy, 1996.
19. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.

20. Wagner H et al. Immunstimulierend wirkende Polysaccharide (Heteroglykane) aus höheren Pflanzen. *Arzneimittel-Forschung*, 1985, 7:1069–1075.
21. Delaveau P et al. Drogues végétales stimulant l'activité phagocytaire du système réticulo-endothélial. *Planta Medica*, 1980, 40:49–54.
22. Janssen AM et al. Screening for antimicrobial activity of some essential oils by the agar overlay technique. *Pharmaceutisch Weekblad*, 1986, 8:289–292.
23. Tarle D, Dvorzak I. Antimicrobial substances in Flos Calendulae. *Farmacevtski Vestnik* (Ljubljana), 1989, 40:117–120.
24. Rios JL, Recio MC, Villar A. Antimicrobial activity of selected plants employed in the Spanish Mediterranean area. *Journal of Ethnopharmacology*, 1987, 21:139–152.
25. Dornberger K, Lich H. Screening for antimicrobial and presumed cancerostatic plant metabolites. *Pharmazie*, 1982, 37:215–221.
26. Acevedo JG, Lopez JL, Cortes GM. In vitro antimicrobial activity of various plant extracts used by purepecha against some Enterobacteriaceae. *International Journal of Pharmacognosy*, 1993, 31:61–64.
27. Kubas J. Investigations on known or potential antitumoral plants by means of microbiological tests. Part III. Activity of some cultivated plant species in *Neurospora crassa* test. *Acta Biologica Cracoviensia Series Botanica*, 1972, 15:87–100.
28. Racz G et al. Trichomonicidal and anthelmintic activity of Roumanian folkloric plants. *Planta Medica*, 1980, 39:257A.
29. Gracza L. Oxygen-containing terpene derivatives from *Calendula officinalis*. *Planta Medica*, 1987, 53:227.
30. Bogdanova NS et al. Study of antiviral properties of *Calendula officinalis*. *Farmakol Toksikol* (Moscow), 1970, 33:349.
31. May G, Willuhn G. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. *Arzneimittel-Forschung*, 1978, 28:1–7.
32. Kalvatchev Z et al. Anti-HIV activity of extracts from *Calendula officinalis* flowers. *Biomedicine and Pharmacotherapy*, 1997, 51:176–180.
33. Fokina GI et al. Experimental therapy of tick-borne encephalitis. *Soviet Progress in Virology*, 1991, 1:27–31.
34. Della-Loggia R et al. The role of triterpenoids in the topical anti-inflammatory activity of *Calendula officinalis* flowers. *Planta Medica*, 1994, 60:516–520.
35. Akihisa T et al. Triterpene alcohols from the flowers of Compositae and their antiinflammatory effects. *Phytochemistry*, 1996, 43:1255–1260.
36. Zitterl-Eglseer K et al. Anti-oedematous activities of the main triterpendiol esters of marigold (*Calendula officinalis* L.). *Journal of Ethnopharmacology*, 1997, 57:139–144.
37. Peyroux J et al. Anti-oedemic and anti-hyperhaemic properties of *Calendula officinalis* L. *Plantes médicinales et Phytotherapie*, 1981, 15:210–216.

38. Mascolo N et al. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytotherapy Research*, 1987, 1:20–31.
39. Bezakova L et al. Inhibitory activity of isorhamnetin glycosides from *Calendula officinalis* L. on the activity of lipoxygenase. *Pharmazie*, 1996, 51:126–127.
40. Rao SG et al. *Calendula* and *Hypericum*: two homeopathic drugs promoting wound healing in rats. *Fitoterapia*, 1991, 62:508.
41. Patrick KFM et al. Induction of vascularisation by an aqueous extract of the flowers of *Calendula officinalis* L., the European marigold. *Phytomedicine*, 1996, 3:11–18.
42. Livezey A. Some observations on our indigenous medical flora. *Medical and Surgical Reporter*, 1868, 19:85.
43. Reynolds RG. *Calendula*. *Pacific Medical and Surgical Journal*, 1886, 29:720.
44. Elias R et al. Antimutagenic activity of some saponins isolated from *Calendula officinalis* L., *C. arvensis* L. and *Hedera helix* L. *Mutagenesis*, 1990, 5:327–331.
45. Avramova S et al. Source of new products for the cosmetic industry. *Medical and Biological Information*, 1988, 4:28–32.
46. Ramos A et al. Genotoxicity of an extract of *Calendula officinalis* L. *Journal of Ethnopharmacology*, 1998, 61:49–55.
47. Bruynzeel DP et al. Contact sensitization by alternative topical medicaments containing plant extracts. *Contact Dermatitis*, 1992, 27:278–279.
48. Willuhn G. Pflanzliche Dermatika, eine kritische Übersicht. *Deutsche Apotheker Zeitung*, 1992, 132:1873–1883.
49. Van Hellemont J. *Fytotherapeutisch compendium*, 2nd ed. Utrecht, Bohn, Scheltema & Holkema, 1988:113–114.
50. Hänsel R et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Bd. 4: Drogen A-K*, 5th ed. Berlin, Springer-Verlag, 1994.

Flos Chamomillae*

Definition

Flos Chamomillae consists of the dried flowering heads of *Chamomilla recutita* (L.) Rauschert (Asteraceae) (*1–4*).

Synonyms

Matricaria chamomilla L., *M. recutita* L., *M. suaveolens* L. (*3*).
In most formularies and reference books, *Matricaria chamomilla* L. is regarded as the correct species name. However, according to the International Rules of Botanical Nomenclature, *Chamomilla recutita* (L.) Rauschert is the legitimate name for this species (*5*). Asteraceae are also known as Compositae.

Selected vernacular names

Baboonig, babuna, babunah camomile, babunj, bunga kamil, camamilla, camomile, chamomile, camomilla, chamomille allemande, campomilla, chamomille commune, camomille sauvage, fleurs de petite camomille, flos chamomillae, german chamomile, hungarian chamomile, Kamille, Kamillen, kamitsure, kamiture, manzanilla, manzanilla chiquita, manzanilla comun, manzanilla dulce, matricaire, matricaria flowers, pin heads, sweet false chamomille, sweet feverfew, wild chamomile (*3*, *6–9*).

Description

Herbaceous annual; 10–30 cm in height, with erect, branching stems and alternate, tripinnately divided leaves below and bipinnately divided leaves above, both types having almost filiform lobes; the capitulum (to 1.5 cm in diameter) comprises 12–20 white ligulate florets surrounding a conical hollow receptacle on which numerous yellow tubular (disk) florets are inserted; the inflorescence is surrounded by a flattened imbricated involucre; fruit small, smooth, yellowish (*3*, *7*, *10*).

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.

Plant material of interest: flower heads

General appearance

Flos Chamomillae consists of conical flower heads, each bearing a few white ligulate florets and numerous yellowish orange to pale yellow tubular or disk florets on conical, narrow hollow receptacles with a short peduncle; disk florets perfect and without a pappus; ray florets pistillate, white, 3-toothed and 4-veined; involucre hemispherical, composed of 20–30 imbricate, oblanceolate and pubescent scales; peduncles weak brown to dusky greenish yellow, longitudinally furrowed, more or less twisted and up to 2.5 cm long; achenes more or less obovoid and faintly 3- to 5-ribbed; pappus none, or slightly membranous crown (*7*, *11*).

Organoleptic properties

Odour, pleasant, aromatic; taste, aromatic and slightly bitter (*1–3*).

Microscopic characteristics

Receptacle and bracteoles with schizogenous secretory ducts; vascular bundles with phloem fibres; spiral, annular and reticulate but pitted vessels; lignified cells at the bases of the ovaries absent; nearly all parts of florets bear composite-type glandular hairs with short, biseriate stalk and enlarged head, formed of several tiers, each of two cells; ovary with longitudinal bands of small mucilage cells; stigma with elongated papillae at the apex; pollen grains, spherical or triangular, with numerous short spines (*3*).

Powdered plant material

Powdered Flos Chamomillae is greenish yellow to yellowish brown; spiny pollen grains numerous, 18–25 µm in diameter; fragments of yellow or white corolla, with polygonal, small epidermal cells having straight or slightly wavy walls, sometimes papillosed, and sometimes bearing glandular hairs of composite type; fragments of the fibrous layer of anther; fragments from ovary, with glandular hairs and rows of small mucilage cells; green fragments of parenchyma of involucre; stigma with papillae; cells of the achenes with scalariform perforations in walls; fragments of fibrovascular bundles with spiral, annular and reticulate vessels and sclerenchyma fibres; fragments of involucral bracts with epidermis having elliptical stomata up to 30 µm in length, also vessels and fibres; occasional fibre from the stems; minute cluster crystals of calcium oxalate, up to 10 µm in diameter; fragments of lignified parenchyma of the filaments and occasional fragments of vessels (*3*, *7*, *10*).

Geographical distribution

The plant is indigenous to northern Europe and grows wild in central European countries; it is especially abundant in eastern Europe. Also found in western Asia, the Mediterranean region of northern Africa, and the United States of America. It is cultivated in many countries (*3*, *7–13*).

General identity tests

The drug is identified by its macroscopic and microscopic characteristics, and by thin-layer chromatography (*1–3*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Flos Chamomillae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*1*, *14*, *15*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml. Preparations for external use: aerobic bacteria—not more than 10^2/g or ml; fungi—not more than 10^2/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^1/g or ml.

Foreign organic matter

Not more than 10% stems and not more than 2% foreign organic matter (*3*). No flowering heads of *Anthemis cotula* L. or *A. nobilis* L. (*7*).

Total ash

Not more than 13% (*2*).

Acid-insoluble ash

Not more than 4% (*11*).

Moisture

Not more than 12% (*12*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Flos Chamomillae is not more than 0.05 mg/kg (*1*). For other pesticides, see WHO guidelines

on quality control methods for medicinal plants (*14*) and guidelines for predicting dietary intake of pesticide residues (*16*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*14*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*14*).

Other tests

Chemical, dilute ethanol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

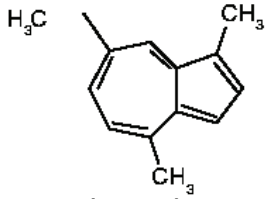
Chemical assays

Contains not less than 0.4% v/w of essential oil (*1–3*). Total volatile oil content is determined by pharmacopoeial methods (*1–3*).

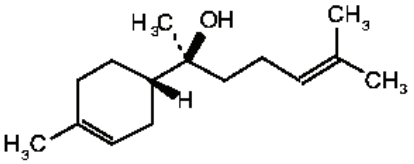
Thin-layer (*1*, *2*) and gas–liquid (*17*) chromatography for volatile oil constituents, and high-performance liquid chromatography for flavonoids (*18*, *19*).

Major chemical constituents

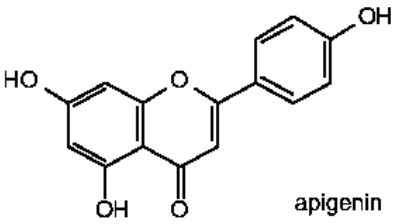
Flos Chamomillae contains an essential oil (0.4–1.5%), which has an intense blue colour owing to its chamazulene content (1–15%). Other major constituents include α-bisabolol and related sesquiterpenes (up to 50% of the oil). Apigenin and related flavonoid glycosides constitute up to 8% (dry weight) of the drug (*10*, *18*).



chamazulene



(−)-α-bisabolol



apigenin

Dosage forms

Dried flower-heads, liquid extract (1:1 in 45% alcohol), tinctures and other galenicals (*11*). Store in well-closed containers, protected from light (*1–3*).

Medicinal uses

Uses supported by clinical data

Internal use

Symptomatic treatment of digestive ailments such as dyspepsia, epigastric bloating, impaired digestion, and flatulence (*3*, *7*, *8*, *10*, *11*, *20*, *21*). Infusions of camomile flowers have been used in the treatment of restlessness and in mild cases of insomnia due to nervous disorders (*21*, *22*).

External use

Inflammation and irritations of the skin and mucosa (skin cracks, bruises, frostbite, and insect bites) (*10*, *23*), including irritations and infections of the mouth and gums, and haemorrhoids (*10*, *11*, *20*, *21*, *23*).

Inhalation

Symptomatic relief of irritations of the respiratory tract due to the common cold (*24*).

Uses described in pharmacopoeias and in traditional systems of medicine

Adjuvant in the treatment of minor inflammatory conditions of the gastrointestinal tract (*24*).

Uses described in folk medicine, not supported by experimental or clinical data

As an antibacterial and antiviral agent, an emetic, and an emmenagogue. It is also used to relieve eye strain, and to treat urinary infections and diarrhoea (*13*).

Pharmacology

Experimental pharmacology

Both camomile extract and (–)-α-bisabolol demonstrated antipeptic activity in vitro (*25*, *26*). A hydroalcoholic extract of camomile inhibited the growth of *Staphylococcus aureus, Streptococcus mutans*, group B *Streptococcus*, and *Streptococcus salivarius*, and it had a bactericidal effect in vitro on *Bacillus megatherium* and *Leptospira icterohaemorrhagiae* (*27*). In vitro, the volatile oil of camomile also inhibited *Staphylococcus aureus* and *Bacillus subtilis* (*28*). In vitro, camomile extracts inhibited both cyclooxygenase and lipoxygenase (*29*), and thus the production of prostaglandins and leukotrienes, known inducers of inflammation. Both bisabolol and bisabolol oxide have been shown to inhibit 5-lipoxygenase, but bisabolol was the more active of the two compounds (*30*). Numerous in vivo studies have demonstrated the anti-inflammatory effects of the drug. The antiinflammatory effects of camomile extract, the essential oil, and the isolated constituents have been evaluated in yeast-induced fever in rats and against ultraviolet radiation-induced erythema in guinea-pig models (*31*). The principal antiinflammatory and antispasmodic constituents of camomile appear to be the terpene compounds matricin, chamazulene, (–)-α-bisabololoxides A and B, and (–)-α-bisabolol (*32–39*). While matricin and (–)-α-bisabolol have been isolated from the plant, chamazulene is actually an artefact formed during the heating of the flowers when an infusion or the essential oil is prepared (*10*). The antiinflammatory effects of these compounds in various animal models, such as inhibition of carrageenin-induced rat paw oedema, have been demonstrated (*30*), although their activity was somewhat less than that of salicylamide (*39*). In the mouse model for croton oil-induced dermatitis, topical application of either the total camomile extract, or the flavonoid fraction only, was very effective in reducing inflammation (*34*). Apigenin and luteolin were more active than indometacin and phenylbutazone (*34*). Activity decreased in the following order: apigenin > luteolin > quercetin > myricetin > apigenin-7-glucoside > rutin (*34*). The spasmolytic activity of camomile has been attributed to apigenin, apigenin-7-*O*-glucoside (*10*, *36*) and (–)-α-bisabolol, which have activity similar to papaverine (*10*, *35*).

Intradermal application of liposomal apigenin-7-glucoside inhibited, in a dose-dependent manner, skin inflammations induced in rats by xanthine oxidase and cumene hydroperoxide (*38*).

Intraperitoneal administration to mice of a lyophilized infusion of camomile decreased basal motility, exploratory and motor activities, and potentiated hexobarbital-induced sleep (*40*). These results demonstrated that in mice camomile depresses the central nervous system (*40*).

Clinical pharmacology

A double-blind study of the therapeutic effects of a camomile extract on re-epithelialization and drying of wound weeping after dermabrasion demonstrated a statistically significant decrease in the wound size and drying tendency (*41*).

In clinical trials, topical application of a camomile extract in a cream base was found to be superior to hydrocortisone 0.25% for reducing skin inflammation (*42*). In an international multicentre trial camomile cream was compared with hydrocortisone 0.25%, fluocortin butyl ester 0.75% and bufexamac 5% in the treatment of eczema of the extremities (*42*). The camomile cream was shown to be as effective as hydrocortisone and superior to the other two treatments, but no statistical analysis was performed. Camomile preparations have also been found to be beneficial in the treatment of radiation mucositis owing to head and neck radiation and systemic chemotherapy (*43*).

Contraindications

Camomile is contraindicated in patients with a known sensitivity or allergy to plants of the Asteraceae (Compositae) such as ragweed, asters, and chrysanthemums (*21*).

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

No mutagenic effects were found in *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA104, with or without metabolic activation (*44*).

Pregnancy: teratogenic effects

No adverse effects reported in vivo (*45*).

Other precautions

No information available concerning general precautions, drug interactions, drug and laboratory test interactions, non-teratogenic effects on pregnancy, nursing mothers, or paediatric use.

Adverse reactions

The presence of lactones in Flos Chamomillae-based preparations may cause allergic reactions in sensitive individuals and there have been reports of contact dermatitis due to camomile preparations (*46–48*). It should be noted that very few cases of allergy were specifically attributed to German camomile (*49*). A few cases of anaphylactic reactions to the ingestion of Flos Chamomillae have also been reported (*50–52*).

Posology

Internal use

Adult dose of flower head: average daily dose 2–8 g, 3 times a day (*7*, *8*, *11*); of fluid extract 1:1 in 45% ethanol: dose 1–4 ml, 3 times a day (*6*, *11*). Child dose of flower head: 2 g, 3 times daily; of fluid extract (ethanol 45–60%): single dose 0.6–2 ml (*11*). Should not be used by children under 3 years old.

External use

For compresses, rinses or gargles: 3–10% (30–100 g/l) infusion or 1% fluid extract or 5% tincture (*11*). For baths: 5 g/l of water or 0.8 g/l of alcoholic extract. For semisolid preparations: hydroalcoholic extracts corresponding to 3–10% (30–100 g/kg) of the drug. For vapour inhalation: 6 g of the drug or 0.8 g of alcoholic extract per litre of hot water (*11*).

References

1. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1997.
2. *Pharmacopée française*. Paris, Adrapharm, 1996.
3. *African pharmacopoeia*, 1st ed. Lagos, Organization of African Unity, Scientific, Technical & Research Commission, 1985.
4. *Estra farmakope Indonesia*. Jakarta, Cetakan Kedua, Hal 152, Departemen Kesehatan, Republik Indonesia, 1974.
5. Rauschert S. Nomenklatorische Probleme in der Gattung *Matricaria* L. *Folia geobotanica phytotaxonomica*, 1990, 9:249–260.
6. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, August 8, 1995 production (an on-line database avail-

able directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).

7. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, Blakiston, 1950.
8. *The Indian Pharmaceutical Codex. Vol. I. Indigenous drugs*. New Delhi, Council of Scientific & Industrial Research, 1953.
9. Leung A, Foster S. *Encyclopedia of common natural ingredients used in food, drugs, and cosmetics*, 2nd ed. New York, John Wiley, 1996.
10. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
11. *British herbal pharmacopoeia.* London, British Herbal Medicine Association, 1990.
12. *Polish pharmacopoeia*. Warsaw, 1965.
13. Tyler VE, Brady LR, Robbers JE, eds. *Pharmacognosy*, 9th ed. Philadelphia, Lea & Febiger, 1988.
14. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
15. *Deutsches Arzneibuch 1996. Vol. 2. Methoden der Biologie*. Stuttgart, Deutscher Apotheker Verlag, 1996.
16. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (unpublished document WHO/FSF/FOS/97.7; available from Food Safety, WHO, 1211 Geneva 27, Switzerland).
17. Carle R, Fleischhauer I, Fehr D. Qualitätsbeurteilung von Kamillenölen. *Deutsche Apotheker Zeitung*, 1987, 127:2451–2457.
18. Dölle B, Carle R, Müller W. Flavonoidbestimmung in Kamillenextraktpräparaten. *Deutsche Apotheker Zeitung*, 1985, 125(Suppl. I):14–19.
19. Redaelli C, Formentini L, Santaniello E. Reversed-phase high-performance liquid chromatography analysis of apigenin and its glucosides in flowers of *Matricaria chamomilla* and chamomille extracts. *Planta medica*, 1981, 42:288–292.
20. Carle R, Isaac O. Die Kamille-Wirkung and Wirksamkeit. *Zeitschrift für Phytotherapie*, 1987, 8:67–77.
21. Carle R, Gomaa K. Chamomile: a pharmacological and clinical profile. *Drugs of today*, 1992, 28:559–565.
22. Gould L, Reddy CVR, Gomprecht RF. Cardiac effect of chamomile tea. *Journal of clinical pharmacology*, 1973, 13:475–479.
23. Hormann HP, Korting HC. Evidence for the efficacy and safety of topical herbal drugs in dermatology. Part 1. Anti-inflammatory agents. *Phytomedicine*, 1994, 1:161–171.
24. Weiß RF. Kamille — "Heilpflanze 1987". *Kneipp-Blätter*, 1987, 1:4–8.
25. Thiemer VK, Stadler R, Isaac O. Biochemische Untersuchungen von Kamilleninhaltsstoffen. *Arzneimittel-Forschung*, 1972, 22:1086–1087.

26. Isaac O, Thiemer K. Biochemische Untersuchungen von Kamilleninhaltsstoffen. *Arzneimittel-Forschung*, 1975, 25:1086–1087.
27. Cinco M et al. A microbiological survey on the activity of a hydroalcoholic extract of chamomile. *International journal of crude drug research*, 1983, 21:145–151.
28. Aggag ME, Yousef RT. Study of antimicrobial activity of chamomile oil. *Planta medica*, 1972, 22:140–144.
29. Wagner H, Wierer M, Bauer R. In vitro inhibition of prostaglandin biosynthesis by essential oils and phenolic compounds. *Planta medica*, 1986:184–187.
30. Ammon HPT, Kaul R. Pharmakologie der Kamille und ihrer Inhaltsstoffe. *Deutsche Apotheker Zeitung*, 1992, 132(Suppl. 27):3–26.
31. Jakovlev V et al. Pharmacological investigations with compounds of chamomile. II. New investigations on the antiphlogistic effects of (–)-α-bisabolol and bisabolol oxides. *Planta medica*, 1979, 35:125–240.
32. Jakovlev V, Isaac O, Flaskamp E. Pharmakologische Untersuchungen von Kamilleninhaltsstoffen. VI. Untersuchungen zur antiphlogistischen Wirkung von Chamazulen und Matricin. *Planta medica*, 1983, 49:67–73.
33. Tubaro A et al. Evaluation of anti-inflammatory activity of chamomile extract after topical application. *Planta medica*, 1984, 51:359.
34. Della Loggia R. Lokale antiphlogistische Wirkung der Kamillen-Flavone. *Deutsche Apotheker Zeitung*, 1985, 125(Suppl. 1):9–11.
35. Della Loggia R et al. Evaluation of the anti-inflammatory activity of chamomile preparations. *Planta medica*, 1990, 56:657–658.
36. Lang W, Schwandt K. Untersuchung über die glykosidischen Bestandteile der Kamille. *Deutsche Apotheker Zeitung*, 1957, 97:149–151.
37. Mann C, Staba J. The chemistry, pharmacology, and commercial formulations of chamomile. In: Craker LE, Simon JE, eds. *Herbs, spices, and medicinal plants: recent advances in botany, horticulture and pharmacology*, Vol. I. Phoenix, AZ, Oryx Press, 1986:233–280.
38. Fuchs J, Milbradt R. Skin anti-inflammatory activity of apigenin-7-glucoside in rats. *Arzneimittel-Forschung*, 1993, 43:370–372.
39. Albring M et al. The measuring of the anti-inflammatory effect of a compound on the skin of volunteers. *Methods and findings in experimental and clinical pharmacology*, 1983, 5:75–77.
40. Della Loggia R et al. Depressive effects of *Chamomilla recutita* (L.) Rausch. tubular flowers, on central nervous system in mice. *Pharmacological research communications*, 1982, 14:153–162.
41. Glowania HJ, Raulin C, Svoboda M. The effect of chamomile on wound healing—a controlled clinical-experimental double-blind study. *Zeitschrift für Hautkrankheiten*, 1986, 62:1262–1271.
42. Aertgeerts P et al. Vergleichende Prüfung von Kamillosan® Creme gegenüber steroidalen (0.25% Hydrocortison, 0.75% Fluocortinbutylester) und nicht-

steroidalen (5% Bufexamac) Externa in der Erhaltungstherapie von Ekzemerkrankungen. *Zeitschrift für Hautkrankheiten*, 1985, 60:270–277.
43. Carl W, Emrich LS. Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients. *Journal of prosthetic dentistry*, 1991, 66:361–369.
44. Rivera IG et al. Genotoxicity assessment through the Ames test of medicinal plants commonly used in Brazil. *Environmental toxicology and water quality*, 1994, 9:87–93.
45. Leslie GB, Salmon G. Repeated dose toxicity studies and reproductive studies on nine Bio-Strath herbal remedies. *Swiss medicine*, 1979, 1:1–3.
46. Dstychova E, Zahejsky J. Contact hypersensitivity to camomile. *Ceskoslovenska dermatologie*, 1992, 67:14–18.
47. Subiza J et al. Allergic conjunctivitis to chamomile tea. *Annals of allergy*, 1990, 65:127–132.
48. Paulsen E, Andersen KE, Hausen BM. Compositae dermatitis in a Danish dermatology department in one year. *Contact dermatitis*, 1993, 29:6–10.
49. Hausen BM, Busker E, Carle R. Über das Sensibilisierungsvermögen von Compositenarten. VII. Experimentelle Untersuchungen mit Auszügen und Inhaltsstoffen von *Chamomilla recutita* (L.) Rauschert und *Anthemis cotula* L. *Planta medica*, 1984:229–234.
50. Benner MH, Lee HJ. Anaphylactic reaction to chamomile tea. *Journal of allergy and clinical immunology*, 1973, 52:307–308.
51. Casterline CL. Allergy to chamomile tea. *Journal of the American Medical Association*, 1980, 244:330–331.
52. Subiza J et al. Anaphylactic reaction after the ingestion of chamomile tea: a study of cross-reactivity with other composite pollens. *Journal of allergy and clinical immunology*, 1989, 84:353–358.

Herba Chelidonii

Definition

Herba Chelidonii consists of the dried, whole or cut aerial parts of *Chelidonium majus* L. (Papaveraceae), gathered during the flowering period (*1–5*).

Synonyms

Chelidonium vulgare Renault, nom. illeg.: *C. haematodes* Moench, *C. ruderale Salisb.*, *C. umbelliferum* Stokes (*6*).

Selected vernacular names

Aekitongpool, Asian celandine, bai qu cai, Blutkraut, büyük halile, celandine, celidonia, cenerognola maggiore, chelidoine, chelidonia maggiore, chelidonium, christessishla, cinerognola, common celandine, devil's milk, eclaire, erba da porri, erba nocca, felougue, garden celandine, gelbes millkraut, gemeines schöllkraut, glistinik jaskólze maistra, Goldwurz, grande chélidoine, grande-éclair, greater celandine, herbe aux hirondelles, herbe aux verrues, herbe de l'hirondelle, herbe d'éclair, iarbă de negi, jeotpool, kkachidari, kelta ruoho, kirlanĝic otu, kusanowo, mamiran, mimirân, otompui kina, paekgoolchae, pilewort, rangui-goli, rostopască, schellkraut, schillkraut, schölkraut, schwalbenwurtz, ssiatong, stinkende gouwe, strutene, svalert, swallow-wort, ta-ukogi, tetterwort, tiges de chelidonine, true celandine, tshistotel, urûq es sabbâghin, urûq surf, vereurmarohi, volosnik, warzenkraut, wulstkraut, ziele glistnika (*7–23*).

Geographical distribution

Indigenous to all of Europe and to the temperate and subarctic regions of Asia, and northern Africa. Found widely in Caucasia and the European part of the Newly Independent States, rare in Siberia and the Far East (*7–9*, *14*, *16*, *24–28*).

Description

A herbaceous biennial or perennial, 30–100(120) cm high. Rhizome: vertical, thick, fleshy, branched into numerous roots, reddish-brown outside, yellow

inside. Stem: erect, irregularly bifurcated, with thickened nodes, glabrous above and hairy beneath (especially on the nodes). Leaves: alternate, compound, pinnate-pinnatifid or bipinnatifid, coarsely crenate or dentate margins, hairless to mostly hairless, upper surface dull green, lower surface pale green, with conspicuous veins, very thin in texture and drooping immediately upon gathering, up to 16 cm long and 8 cm wide. Each compound leaf typically has 5 leaflets, sometimes 3 (apical leaflet is usually larger), which are pinnatifid with secondary lobes, ovate or obovate in overall shape; secondary lobes have blunt tips. Lower leaves petiolated, upper leaves sessile. Rachis and petioles may have a few scattered hairs. Inflorescences, loose umbels of 3–8 flowers; flowering stalks 5–10 cm long; develop oppositely from the compound leaves. Flowers, actinomorphous, 4 yellow petals, 2 sepals that fall early, 1.2–1.8 cm in diameter, pistil with a stout style and elongated ovary, and numerous yellow stamens. Pedicels, 1.2–2.5 cm long. Fruits, slender siliqua-like capsules, ascending, monolocular, many seeded, linear-cylindrical, 2–5 cm long, tapering gradually towards the apex, outer surface is smooth, glaucous and hairless. As the fruit matures, it becomes constricted at intervals, dehiscing by two valves from the bottom. Seeds, ovoid, flattened glossy, black-brown with small white appendages. The whole plant abounds in bright, orange-coloured latex, which is emitted wherever the leaves or stems are broken. The juice stains hands strongly, has a persistent and nauseous taste, a strongly disagreeable smell, and burns the skin and eyes. The whole plant is poisonous (*1*, *7*, *11*, *24*, *29–36*).

Plant material of interest: dried aerial parts

General appearance

Whole or cut leafed stems with flowers, and unripe and/or ripe fruits, pieces of stems, leaves, flowers and fruits. Stems are rounded, ribbed, thin-walled, sometimes branched, whole at internodes, somewhat pubescent, yellowish to greenish-brown or olive green, up to 50 cm long and about 3–7 mm in diameter. Leaf fragments, mainly glabrous, bluish-green and glabrous on one side, and pale green and pubescent on the veins on the other side. Yellow flowers with 2 readily removed membranous sepals, 4 obovate petals, one pistil, and numerous stamens. Fruit, linearcylindrical, siliqua-like capsules. Seeds, small, numerous, ovate, rough, brown-black (*1*, *2*, *5*).

Organoleptic properties

Odour: peculiar and irritating, the latex has a narcotic fragrance; taste: very bitter and somewhat pungent (*5*, *7*, *24*, *29*).

Microscopic characteristics

The transverse section of the stem is circular, lightly ribbed, covered by a thin cuticle. The epidermal cells have very thick walls. One or two layers of thin-walled chlorenchymatous hypodermis partly transformed into collenchyma. Cortex consists of polygonal, very thick-walled cells (sclerenchyma). Very few covering trichomes of 5–10 cells, long, uniseriate, thin-walled. Stomata anomocytic, not numerous. The petiole has a stem-like structure. The chlorenchyma is almost entirely transformed in collenchyma. There are multicellular, very long covering trichomes. Leaf epidermis with sinuous anticlinal walls. Very few covering trichomes, long, uniserate of 5–10(20) thin-walled cells (striated cells, cellular nucleus visible). Area with papilla on the epidermis. Stomata anomocytic, exclusively on the lower epidermis. Hydathodes at the lobed margins. The mesophyll is differentiated into a layer of palisade and two layers of spongy parenchyma (transverse section), made up of thin-walled chlorenchyma. Cells of spongy parenchyma have aquifer stomata. Midrib with 1- or 2-layered collenchyma below the upper epidermis and thin-walled parenchymatous ground tissue. Palisade ratio 7.6:13.22. Calcium oxalate absent. Larger veins associated with dark brown articulated non-branched laticifers. Latex cells especially in vascular region. Pollen grains spherical, with a finely pitted exine and 3 furrows, about 35 µm in diameter (*2*, *5*, *30*, *37–39*).

Powdered plant material

The powder shows the characteristic elements of stems, leaves and flowers: numerous fragments of leaves, the epidermal cells with sinuous walls; anomocytic stomata occur on the abaxial surface only; fragments of covering trichomes or entire ones. Groups of vascular tissue from the petiole and main veins with attached laticifers.

General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography, paper chromatography and high-performance liquid chromatography for the presence of the characteristic alkaloids (*1*, *2*, *12*, *40*). The addition of two or three drops of Mayer reagent to the acidic extract results in a purple precipitation of needles (*14*). Addition of two or three drops of Dragendorff's reagent to the acidic extract results in a yellow precipitate (*41*). Under ultraviolet light at 365 nm without treatment, the thin-layer chromatogram of Herba Chelidonii usually shows 2 or 3 blue and yellow-green fluorescent zones at Rf approximately 0.2; directly above this is the narrow yellow-green zone of chelerythrine, followed by the tailing

yellow zone of sanguinarine. The pale white fluorescent zone of protopine is located in the same position as standard berberine: this is usually overlapped by sanguinarine after treatment with Dragendorff-sodium nitrite; chelidonine (Rf approximately 0.6) and the other alkaloids from rapidly fading brown zones. Papaverine can be used for the comparison of Rf values (*42*). The addition of 1 ml of Dragendorff's reagent to the dried residue of a chloroform extract results in a golden precipitate. Addition of one drop of chloroform extract to the filter paper shows an area of fluorescence under an ultraviolet lamp (*43*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*44*).

Chemical

No information available.

Foreign organic matter

Not more than 1% of organic matter. Not more than 3% of aerial parts with non-natural colour (*2*).

Total ash

Not more than 13% (*1*). Not more than 15% (*2*, *5*).

Acid-insoluble ash

Not more than 2% (*2*, *5*).

Sulfated ash

No information available.

Water-soluble extractive

Not less than 20% (*5*).

Alcohol-soluble extractive

No information available.

Loss on drying

Not more than 10% (*1*). Not more than 14% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg. For other pesticides, see the *European pharmacopoeia* (*1*), and the WHO guidelines on quality control methods for medicinal plants (*44*) and the WHO guidelines on pesticide residues (*45*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*44*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*44*) for the analysis of radioactive isotopes.

Other purity tests

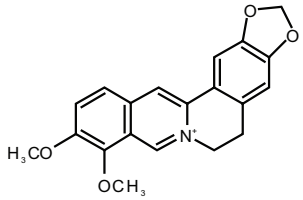
Not more than 10% of foreign matter (*1*). Not more than 0.5% of mineral matter (*2*). Chemical, sulfated ash, and alcohol-soluble extractive to be established in accordance with national requirements.

Chemical assays

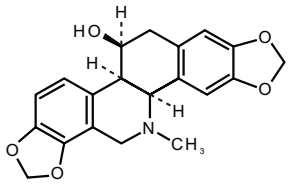
Contains not less than 0.6% of total alkaloids, expressed as chelidonine (*1*). Contains not less than 0.2% of total alkaloids, expressed as chelidonine, and assayed by potentiometric titration (*2*).

Major chemical constituents

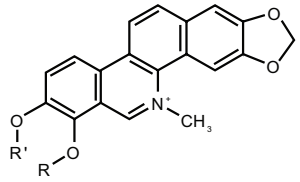
The major constituents of dried aerial parts are alkaloids in an orange-coloured latex (*5*). They contain 0.1–1.30% total alkaloids (> 20 bases of the benzophenanthridine and related groups); quantitatively the most important are chelidonine, sanguinarine, coptisine and chelerythrine; also present are berberine, protopine (*7*), homochelidonine (*24*), allocryptopine (*4*), stylopine, oxysanguinarine, chelirubine (*14*, *15*, *46*), turkiyenine and canadine (*47*, *48*). The plant also contains flavonoids, saponins, organic acids, vitamins, carotenoids, tyramine and several hydroxycinnamic acid derivatives including caffeoylmalic, chelidonic, malic and citric acids have also been reported. Proteolytic enzymes have been detected in the latex (*4*, *7*, *14*, *15*, *25–27*, *41*, *49–52*). The roots contain alpha-spinasterol, and the leaves 1-hexacosanol (*41*). The newly identified cysteine-proteinase, chelidocystatin has been isolated (*53*). The structures of the major constituents are presented below.



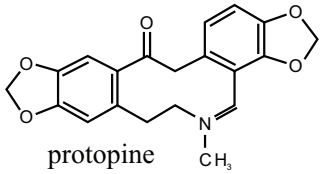
berberine



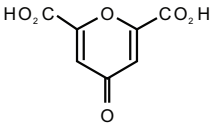
chelidonine



chelerythrine R = R' = CH_3
sanguinarine R + R' = CH_2



protopine



chelidonic acid

Medicinal uses

Uses supported by clinical data

Used for the symptomatic treatment of mild to moderate spasms of the upper gastrointestinal tract, minor gallbladder disorders, and dyspeptic complaints such as bloating and flatulence (*54–56*).

Uses described in pharmacopoeias and well established documents

Used externally as an anti-inflammatory agent (*2*).

Uses described in traditional medicine

Used for the treatment of vision disorders, gallstones, jaundice, irritable bowel syndrome, migraine, ringworm, whooping cough and warts (*57–60*). In Chinese medicine Herba Chelidonii is used as an anti-inflammatory agent in the treatment of oedemas, inflammation of the eyelids, and in ulcerative dermatitis (*29*).

Pharmacology

Experimental pharmacology

Antihepatotoxic activity

An aqueous-ethanolic extract of Herba Chelidonii, containing 41–45% of ethanol exerted significant hepatoprotective activity against carbon tetrachloride (CCl_4) toxicity in rats treated with varying doses of the extract.

Intragastric administration of 12.5, 62.5 and 125 mg/kg body weight (bw) of the extract twice weekly over 3 weeks resulted in a reduction in CCl_4-induced hepatotoxicity. Increased plasma activities of the enzymes alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and lactate dehydrogenase, as well as the increased bilirubin level, induced by CCl_4, were significantly decreased by the extract. The liver tissue appeared free from fibrosis, and cholesterol, which first decreased as a result of treatment with CCl_4, significantly increased during the treatment with the extract. Histopathological evaluation of the liver cells indicated a marked reduction in the number of necrotic cells (*61*). However, it is difficult to evaluate the clinical significance of these findings with regard to hepatotoxic adverse reactions (see Adverse reactions).

Anti-inflammatory activity

An extract made from a tincture of crude drug, as well as the individual alkaloids chelidonine, berberine, chelerythrine and sanguinarine, were tested in an anti-inflammatory enzyme assay in vitro to determine their ability to inhibit 5- and 12-lipoxygenases (5-LOX and 12-LOX), two enzymes in the inflammatory cascade. The two most active inhibitors of both enzymes were the quaternary alkaloids, sanguinarine (median inhibitory concentration (IC_{50}) = 0.4 µM for 5-LOX and 13 µM for 12-LOX) and chelerythrine (IC_{50} = 0.8 µM for 5-LOX and 33 µM for 12-LOX). Chelidonine and berberine were inactive. An extract containing 0.68% total alkaloids, calculated as chelidonine inhibited 5-LOX activity with an IC_{50} of 1.9 µM (based on the molecular weight of chelidonine) (*62*).

Antispasmodic activity

The effects of two dry ethanol extracts of the herb with a defined content of the main alkaloids (chelidonine, protopine and coptisine), and the alkaloids themselves were assessed in three different antispasmodic tests using ileum isolated from guinea-pigs. When ileal contractions were stimulated by barium chloride, both extracts reduced contractions, the more concentrated extract by 53.5% and the less concentrated by 49%, when added to the bath media at a concentration of 500 µg/ml. In addition, both chelidonine and protopine exhibited papaverine-like musculotropic action, whereas coptisine (in concentrations of up to 30 µg/ml) was ineffective in this model. Both carbachol and electrical-field-stimulated contractions were also reduced by all three alkaloids. The IC_{50} of the crude drug extracts in carbachol- and electrical-field-induced ileal spasms were in the range of 250–500 µg/ml (*63*). An aqueous-ethanol extract of the herb containing 0.81% total alkaloids, calculated as coptisine, as well as the individual compounds,

caffeoylmalic acid and coptisine, were examined for their activity against acetylcholine-induced contractions in ileum isolated from rats. Acetylcholine-induced contractions were slightly reduced by the extract (12.7%; 2 mg/ml), and by coptisine (16.5%; 0.1 mg/ml) (*64*). In another study, acetylcholine-induced contractions in isolated guinea-pig ileum were antagonized by the addition of protopine and allocryptopine (IC_{50} 2.3 µM) to the bath media, whereas berberine potentiated the contractions (*65*).

Choleretic activity

The choleretic activity of an ethanol extract of the herb was assessed in isolated perfused rat liver. The extract (70% ethanol v/v, 5:1, 1.6% total alkaloids and 1.9% hydroxycinnamic acid derivatives), as well as separated alkaloid and phenolic fractions of the extract, increased bile flow. A 70% ethanol extract of the herb significantly ($p < 0.05$) increased bile flow by 20% after pretreatment (40 minutes) at a concentration of 10 mg/ml (*66*).

Central nervous system effects

The effects of a 95% ethanol extract of the herb on the modulation of γ-aminobutyric acid- (GABA-)activated chloride current in acutely dissociated periaqueductal grey neurons were investigated using the nystatin-perforated patch-clamp technique. High concentrations of the extract (150 µg/ml) elicited an ion current that was blocked by bicuculline. Lower concentrations of the extract (90 µg/ml) reduced the GABA-activated current which operates through G-proteins in periaqueductal grey neurons (*67*).

The effect of a dry ethanol extract (95%) of the herb on the binding of radiolabelled muscimol to the GABA-A receptor was investigated in the brain cortex of male rats in vitro. At a concentration of 90 µg/assay, the extract enhanced [3H]-muscimol-specific binding by 115%, while 160 g/assay of the extract exerted a 50% inhibition of the specific binding of [3H]-muscimol. The allosteric modulation of the GABA-A receptor by the crude extract was due to the presence of protopine. Specific binding of [3H]-muscimol was inhibited only by sanguinarine and chelerythrine, with IC_{50} values of 25 µM and 39 µM, respectively. However, the concentration of chelerythrine and sanguinarine in the extract was too low to account for the observed effect of the extract on [3H]-muscimol binding to the GABA-A receptor (*68*).

Antitumour activity

The effects of an extract of the herb on the development of gastric tumours in rats were assessed after the administration of *N*-methyl-*N*'nitro-*N*-nitrosoguanidine (MNNG). Sixty-four male 6-week-old

rats were divided into three groups: rats in group 1 were initially given MNNG (200 mg/kg bw) by gavage at days 0 and 14 as well as saturated sodium chloride solution (1 ml per rat) every three days during weeks 0–3 (six doses in total), and were then fed a regular diet containing 0.1% of the extract for 16 weeks starting at week 4. The rats in groups 2 and 3 were treated with MNNG together with saturated sodium chloride or saline solution (0.9% sodium chloride, 1 ml per rat), respectively, for the same time as those in group 1, but without further treatment. All surviving animals were killed at week 20 and assessed histopathologically. The number of preneoplastic pepsinogen 1 altered pyloric glands in the glandular stomach of the rats treated with MNNG + sodium chloride + extract (0.1%) (group 1) was significantly smaller ($p < 0.02$) than in the rats treated with MNNG + sodium chloride (groups 2 and 3). The incidences of neoplastic lesions of the fore stomach (papillomas and squamous cell carcinomas) also showed a tendency to decrease in the animals that received treatment with the extract. The results suggest that the extract exerts an inhibitory effect on glandular stomach carcinogenesis in the rat (*69*).

CM-Ala, a water-soluble, protein-bound polysaccaharide from *Herba Chelidonii*, demonstrated cytotoxic activity in a diverse group of tumour cells (*70*).

A crude 40% ethanol extract of Herba Chelidonii possessed marked cytotoxicity, suppressing the growth of the human lymphoblastoid Raji cells at concentrations of 10 and 50 µg/ml (*71*).

Ethanolic and aqueous extracts of Herba Chelidonii were evaluated for their cytotoxic activity in the *Artemia salina* lethality bioassay using umbelliferone and colchicine as active substances. No cytotoxicity of the extracts was observed, and the results indicate the safety of Herba Chelidonii for its traditional uses (*72*).

Immune stimulation

The CM-Ala fraction, separated from an aqueous extract of Herba Chelidonii, was tested for immunostimulatory effects, including the generation of activated natural killer cells, proliferation of splenocytes and the activation of macrophages, as well as the assay of granulocyte macrophage colony forming cells. CM-Ala enhanced cytotoxicity against Yac-1 tumour cells from 0.88% to 34.18% after culturing with splenocytes for 5 days. CM-Ala also increased nitric oxide production twofold in peritoneal macrophages and exhibited cytotoxic activity. In addition, CM-Ala demonstrated mitogenic activity in both spleen cells and bone marrow cells, induced an 84-fold increase in the proliferation of splenocytes, and in-

creased the numbers of granulocyte macrophage-colony forming cells 1.48-fold as compared to the untreated splenocytes (*70*).

Toxicology

No harmful or toxic effects from therapeutic doses have been reported in rodent models. In mice, the median lethal dose (LD_{50}) of a decoction of the crude drug was 9.5 g/kg bw after intraperitoneal administration. The LD_{50} of the isoquinoline alkaloids in mice was 300 mg/kg bw after subcutaneous administration. Intraperitoneal administration of 350 mg/kg bw of a methanol extract of the herb to mice for 7 days resulted in a 20% mortality rate (*60*). The median lethal intraperitoneal dose for chelidonine was 1300 mg/kg bw in mice and 2000 mg/kg bw in rats. Sublethal doses of chelidonine induced sedation, ptosis, tremor and decreased body temperature (*73*). The methanol and aqueous extracts of Herba Chelidonii were examined for acute oral toxicity in mice. The LD_{50} for the methanol extract was 12.5 g/kg bw and that for the aqueous extract was 10.1 g/kg bw (*74*). Oral administration of 5 mg/kg bw of sanguinarine and chelerythrine (3:1) to pigs for 90 days did not result in any histological or biochemical changes (*75*).

The alkaloids sanguinarine and chelerythrine, present in low concentrations in the herb, are known to cause hepatotoxicity in rats. Intraperitoneal administration to rats of 10 mg/kg bw of sanguinarine or chelerythrine induced hepatic cell injury and increased alanine aminotransferase and aspartate aminotransferase activities by 50 and 100%, respectively. However, intraperitoneal administration of 0.2 mg/kg bw of sanguinarine or chelerythrine to rats for 55 days did not result in signs of hepatotoxicity (*76*, *77*). Investigation of extracts of the herb, as well as of the individual alkaloids, coptisine, chelidonine, protopine, chelerythrine and sanguinarine, in primary rat hepatocytes indicated a direct correlation between the alkaloid content of the extract and hepatotoxicity. The mean hepatotoxic concentration for the extracts was 5 mg/ml, for sanguinarine 5 µg/ml, and chelerythrine 8 µg/ml.

Clinical pharmacology

A prospective observational study involving 608 patients treated orally with an aqueous-ethanol extract of the crude drug (5–7:1, mean daily dose 375–500 mg extract, corresponding to 9–12 mg of total alkaloids) has been reported. The outcomes were measured using the Physicians' Global Assessment of Efficacy (4-point scale). After an average of 22 days of treatment, symptoms (dyspepsia or cramps in the upper gastrointestinal tract) were reduced in most patients and the outcome was assessed as good or very good in 87.4% of the patients (*55*).

A placebo-controlled, double-blind clinical trial assessed the efficacy of tablets prepared from an aqueous-ethanol extract of the crude drug corresponding to a daily dose of 24 mg of total alkaloids (calculated as chelidonine) in patients suffering from epigastric complaints or cramps in the biliary system and/or the upper gastrointestinal tract. Sixty patients were treated for 14 days with the extract or a placebo. Outcomes measured after 4 and 6 weeks included the global assessment of a clinician and the patient's self-rating according to the von Zerssen Complaint Scale. After 6 weeks of treatment, 60% of the treated patients and 27% of the placebo group were considered to be responders ($p = 0.038$), according to the global assessment of a clinician. The von Zerssen Complaint Scale score was also 15% lower ($p = 0.003$) in patients after treatment with the extract than for those in the group treated with the placebo. The treatment reduced symptoms, such as stomach ache, bile-related complaints, flatulence, nausea and bloating (*56*).

Adverse reactions

Excessive ingestion of the decoction of the crude drug may cause nausea and other gastrointestinal symptoms (*60*). In rare cases, hepatic inflammation and an increase in liver enzyme activity and serum bilirubin have been reported, all of which are reversible following discontinuation of therapy (*78*). A case of contact dermatitis was described after external use of the aerial parts of the plant (*79*). Ten cases of acute hepatitis induced by preparations of the crude drug have been noted. The course of hepatitis was mild to severe. Marked cholestasis was observed in five patients, but liver failure did not occur. Other possible causes of liver disease were excluded by laboratory tests and imaging procedures, and liver biopsy specimens were consistent with drug-induced damage. After discontinuation of therapy, rapid recovery was observed in all patients and liver enzyme levels returned to normal in 2–5 months (*80*). One case of haemolytic anaemia after oral ingestion of an extract of crude drug was reported. Presentation included liver cytolysis, thrombocytopaenia, renal failure and intravascular haemolysis. The direct antiglobulin test was positive. The patient was treated with steroids, red cell and platelet transfusion and subjected twice to haemodialysis, with complete resolution of the clinical features by about the twelfth day (*81*).

Cases of acute hepatitis after use of Herba Chelidonii preparations have been observed (*82*, *83*).

A case of contact-derived allergic balanoposthitis and paraphimosis (lesions of the penis) was observed after topical application of Herba Chelidonii juice (*84*).

Contraindications

In patients with biliary obstructions, existing or previous liver disease or hepatitis, concomitant use of hepatotoxic substances is contraindicated (*80*, *85*).

Warnings

Use of the crude drug and preparations of Herba Chelidonii should be restricted to short-term use (1–4 weeks) and long-term use (for more than 4 weeks) is not recommended. Due to the potential for liver toxicity, liver enzymes should be evaluated prior to and during use (*81*, *86*, *87*). Health professionals should be encouraged to report any suspected adverse reactions thought to be associated with Herba Chelidonii.

Precautions

General

Use only under professional supervision. In patients with gallstones, the product should not be used without medical advice (*4*). The plant is subject to legal restrictions in some countries (*88*, *89*). The Drug and Medicinal Product Institute of Germany recommends a maximum daily dose of 2.5 mg total alkaloids, which is lower than the recommended doses prescribed by other authorities (*3*, *5*, *89*).

Drug interactions

No information was found.

Carcinogenesis, mutagenesis, impairment of fertility

No information was found.

Pregnancy

The use of Herba Chelidonii during pregnancy is not recommended (*90*).

Nursing mothers

The use of Herba Chelidonii while breastfeeding is not recommended (*90*).

Other precautions

No information was found.

Dosage forms

Crude drug, powdered drug for infusions, tablets containing 4 mg total alkaloids (*56*).

Posology

(Unless otherwise prescribed)

Internal use. One to two tablets each containing 4 mg total alkaloids three times a day (*55*, *89*); 2–5 g herb, equivalent to 12–30 mg of total alkaloids calculated as chelidonine (*3*).

External use as a bath. An infusion from two tablespoonfuls of the cut herb added to 500 ml of water per bath (*88*).

References

1. *European Pharmacopoeia*, 5th ed. Strasbourg, Council of Europe, 2005.
2. *USSR State Pharmacopoeia,* 11th ed. Moscow, Ministry of Health, 1998.
3. Blumenthal M et al., eds. *The complete German Commission E monographs. Therapeutic guide to herbal medicines.* Austin, TX, American Botanical Council, 1998.
4. European Scientific Cooperative on Phytotherapy (ESCOP) Monographs. *The scientific foundation for herbal medicinal products*, 2nd ed. New York, Thieme, 2003.
5. *British herbal pharmacopoeia*. Bournemouth, Scientific Committee of the British Medicine Association, 1983.
6. *Northern Ontario Plant Database* (www.northernontarioflora.ca).
7. Bisset NG, Wichtl M. *Herbal drugs and phytopharmaceuticals: A handbook for practice on a scientific basis.* Stuttgart, Medpharm, 1994.
8. *PDR for herbal medicines.* New Jersey, Medical Economics Company, 2000.
9. Bown D. *Encyclopaedia of herbs and their uses*. London, Dorling Kindersley, 1995.
10. Turova AD, Sapohzhnikova EN. *Lekarstvenny'je rastenija SSSR I ikh primenenije.* Moscow, Meditsina, 1982.
11. *Plants for a future* (http://www.ibiblio.org/pfaf/D_search.html).
12. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific Publishers, 2001.
13. Mabberley DJ. *The plant book.* Cambridge, Cambridge University Press, 1997.
14. Han DR et al. *Modern pharmacognosy*. Seoul, Hakchang, 1988.
15. Kim IH et al. *Medicinal botany*. Seoul, Hakchang, 1988.
16. Bedevian AK. Illustrated polyglottic dictionary of plant names. Cairo, Medbouly Library, 1994.
17. Parsa A. *Flore de L'Iran*. *Vol. 8.* Tehran, University of Tehran, 1960.
18. Palade M. *Botanica farmatseutica. Sistematica generala*. Bucharest, Editura Tehnica, 1998.
19. Wren RC. *Potter's new cyclopedia of botanical drugs and preparations.* Saffron Walden, CW Daniel, 1988.

20. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.
21. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
22. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
23. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
24. Grieve M, Leyel CF, eds. *A modern herbal.* London, Tiger Books International, 1998.
25. Muravjova DA. *Farmakognozija.* Moscow, Meditsina, 1991.
26. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija,* Moscow, Meditsina, 2002.
27. Yakovlev GP, Blinova KF, eds. *Lekarstvennoje rastitel'noje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
28. Muravjova DA, R'batshuk IZ. *Farmakognozija*. Moscow, Meditsina, 1984.
29. Fleming T, ed. *Physicians' desk reference (PDR) for herbal medicines*. Montvale, Medical Economics Company, 2000.
30. *Homoeopathic pharmacopoeia of India*. *Vol. 4*, 1st ed. Government of India, Ministry of Health, 1983.
31. Bunney S, ed. *The illustrated encyclopaedia of herbs: their medicinal and culinary uses.* London, Chancellor Press, 1993.
32. Petkov V, ed. *Sovremennaja fitoterapija.* Sofia, Meditsina i fizkultura, 1988.
33. Comarov VL, Shishkin BK. *Flora SSSR*. *Vol. 25.* Pod red. Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1959.
34. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR. Izd.* Moscow, Mysli, 1976.
35. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR*. 3-ie izd. Kishinev, Shtiintsa, 1986.
36. *Botaniceskii atlas*. Moscow, Seliskohozeaistvennoi Literatury, Jurnalov i Plakatov, 1963.
37. Toma C, Rugina R. *Anatomia plantelor medicinale. Atlas***.** Bucharest, Editura Academei Romane, 1998.
38. Grigorescu E, Stanescu U. *Farmacognozie*. *Vol. 2*. Bucharest, Iasi, 1977.
39. Grinkevici NI, Ladiginoi EI, eds. *Pharmacognozia. Atlas*. Pod red. Moscow, Meditsina, 1989.
40. Mukherjee PK. *Quality control of herbal drugs: an approach to evaluation of botanicals.* New Delhi, Horizons Pharmaceutical Publishers, 2002.
41. Ji OP et al. *Pharmacognosy*. Seoul, Hakchang, 2005.
42. Wagner H, Bladt S, Zgainski EM. *Plant drug analysis – a thin layer chromatography atlas.* Berlin, Springer Verlag, 1984.
43. *The Korean herbal pharmacopoeia*. Seoul, Korea Food and Drug Administration, 2002.
44. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.

45. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
46. Choi SZ et al. Cytotoxic constituents of *Chelidonium majus* var. *asiaticum. Saengyak Hakhoechi*, 2001, 32:10–14.
47. Shapiro DK et al. *Rastitel'nye resursy. Vol. 14.* Leningrad, Nauka, 1978.
48. Kadan G, Gozler T, Shamma M. (–)-Turkiyenine, a new alkaloid from *Chelidonium majus. Journal of Natural Products*, 1990, 53:531–532.
49. Wagner H, Bladt S. *Plant drug analysis – a thin layer chromatography atlas*, 2nd ed. New York, Springer Verlag, 1996.
50. Sokolov SY, Zamotajev IP. *Spravotshnik po lekarstvenn'm rastenijam. Fitoterapija*, 2nd ed. Moscow, Meditsina, 1988.
51. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Magnoliaceae-Limoniaceae. Vol. 1.* Leningrad, Nauka, 1984.
52. Wichtl M, ed. Chelidonii herba. In: *Teedrogen und Phytopharmaka,* 3rd ed. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1997, 117:1234–1237.
53. Rogelj B et al. Chelidocystatin, a novel phytocystatin from *Chelidonium majus. Phytochemistry*, 1998, 49:1645–1649.
54. Knöpfel SA. Behandlung von Erkrankungen der Gallenwege und der Gallenblase mit dem natürlichen Cholendynamikum Chelidonin. Auch gegen Gallenleiden ist ein Kraut gewachsen [Treatment of biliary tract and cholecystic diseases with natural bile-excreting Chelidonine. Also a plant can treat diseases of the liver]. *Therapeutikon*, 1991, 5:205–208.
55. Kniebel R, Urlacher W. Therapie krampfartiger Abdominalschmerzen. Hochdosierter Schöllkraut-extrakt bei krampfartigen Abdominalschmerzen [Therapy of spastic abdominal pain. High dose of Chelidonium extract for spastic abdominal pain]. *Zeitschrift für Allgemeine Medizin*, 1993, 69:680–684.
56. Ritter R et al. Clinical trial on standardized celandine extract in patients with functional epigastric complaints: results of a placebo-controlled double-blind trial. *Complementary Therapies in Medicine*, 1993, 1:189–193.
57. Abu Ali Ibn Sina. *Kanon vratchebnoi nauki*. Tashkent, Fan, 1956.
58. Amirdowlat Amasyaci. *Nenuzhnoe dlja neuczej* (*Needless for ignoramus*). Moscow, Nauka, 1990.
59. Zadorozhnyj AM et al. *Spravocznik po lekarstvennim rastenijam*. Moscow, Lesnaja promyshlennost', 1990.
60. Mills S, Bone K. *Principles and practice of phytotherapy: Modern herbal medicine*. Edinburgh, Churchill Livingstone, 2000.
61. Mitra S et al. Antihepatotoxic activity of *Chelidonium majus. International Journal of Pharmacognosy*, 1992, 30:125–128.
62. Vavrecková C, Gawlik I, Müller K. Benzophenanthridine alkaloids of *Chelidonium majus*. 1. Inhibition of 5- and 12-lipoxygenase by a non-redox mechanism. *Planta Medica,* 1996, 62:397–401.

63. Hiller KO, Ghorbani M, Schilcher H. Antispasmodic and relaxant activity of chelidonine, protopine, coptisine, and *Chelidonium majus* extracts on isolated guinea-pig ileum. *Planta Medica*, 1998, 64:758–760.
64. Boegge S et al. Reduction of ACh-induced contraction of rat isolated ileum by coptisine, (+)-caffeoylmalic acid, *Chelidonium majus*, and *Corydalis lutea* extracts. *Planta Medica*, 1996, 62:173–174.
65. Piacente S et al. Different effects of some isoquinoline alkaloids from Argemone mexicana on electrically induced contractions of isolated guinea-pig ileum. *Phytotherapy Research*, 1997, 11:155–157.
66. Vahlensieck U et al. The effect of *Chelidonium majus* herb extract on choleresis in the isolated perfused rat liver. *Planta Medica*, 1995, 61:267–270.
67. Kim Y et al. Modulation of Chelidonii herba on GABA activated chloride current in rat PAG neurons. *American Journal of Chinese Medicine*, 2001, 29:265-279.
68. Haberlein H et al. *Chelidonium majus* l. Components with in vitro affinity for the GABA receptor. Positive cooperation of alkaloids. *Planta Medica*, 1996, 62:227–231.
69. Kim DJ et al. Potential preventive effects on *Chelidonium majus* l. (Papaveraceae) herb extract on glandular stomach tumour development in rats treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and hypertonic sodium chloride. *Cancer Letters*, 1997, 112:203–208.
70. Song JY et al. Immunomodulatory activity of protein-bound polysaccharide extracted from *Chelidonium majus. Archives of Pharmacology*, 2002, 25:158–164.
71. Spiridonov NA et al. Cytotoxicity of some Russian ethnomedical plants and plant compounds. *Phytotherapy Research*, 2005, 19:428–432.
72. Saglam H, Arar G. Cytotoxic activity and quality control determinations on *Chelidonium majus*. *Fitoterapia*, 2003, 74:127–129.
73. Jagiello-Wojtowicz E et al. Preliminary pharmacological evaluation of Chelidonine in rodents. *Polish Journal of Pharmacology and Pharmacy*, 1989, 41:125–131.
74. Kim JH et al. Studies on the acute oral toxicity and anti-inflammatory activity of extract of Chelidonii Herba from Korea. *Herba Chelidonii. Report of CFDSR WonKwang University*, 1995, 8:7–18.
75. Kosina P et al. Sanguinarine and chelerythrine: assessment of safety on pigs in ninety days feeding experiment. *Food and Chemical Toxicology*, 2004, 42:85–91.
76. Dalvi RR. Sanguinarine: its potential as a liver toxic alkaloid present in the seeds of *Agremone mexicana*. *Experientia*, 1985, 41:77–78.
77. Ulrichova J et al. Cytotoxicity of benzo[c]phenanthridinium alkaloids in isolated rat hepatocytes. *Phytotherapy Research*, 1996, 10:220–223.
78. Greving I et al. *Chelidonium majus*: a rare reason for severe hepatotoxic reaction. *Pharmacoepidemiology and Drug Safety*, 1998, 7:566–569.

79. Etxenagusia MA et al. Contact dermatitis from *Chelidonium majus* (Greater celandine). *Contact Dermatitis*, 2000, 43:47.
80. Benninger J et al. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Zeitschrift für Gastroenterologie*, 1999, 117:1234–1237.
81. Pinto-Garcia V et al. Haemolytic anaemia induced by *Chelidonium majus*. Clinical Report. *Sangre*, 1990, 35:401–403.
82. Van Noordwijk J. Dosis solum facit venenum also for herbal products. *Nederlands Tijdschrift voor Geneeskunde*, 2002, 19:100–102.
83. Crijns AP et al. Acute hepatitis after use of a herbal preparation with Greater Celandine (*Chelidonium majus*). *Nederlands Tijdschrift voor Geneeskunde*, 2002, 146:124–128.
84. Farina LA et al. Contact-derived allergic balanoposthitis and paraphimosis through topical application of celandine juice. *Actas Urologicas Espanolas*, 1999, 23:554–555.
85. Strahl S et al. Nekrotisierende Hepatitis nach Einnahme pflanzlicher Heilmittel [Necrotizing hepatitis after intake of a herbal remedy]. *Deutsche Medizinische Wochensschrift*, 123:1410–1414.
86. Stickel F et al. Acute hepatitis induced by Greater Celandine (*Chelidonium majus*). *Scandinavian Journal of Gastroenterology*, 2003, 38:565–568.
87. Rifai K et al. 58-jähriger Patient mit schwerer cholestatischer Hepatitis [58 year old patient with severe cholestatic hepatitis]. *Der Internist*, 2006, 47:749–751.
88. Ladynina EA, Morozova RS. *Fitoterapija*, Leningrad, Meditsina, 1987.
89. Hänsel R et al., eds. Chelidonii herba. In: *Hagers Handbuch der Pharmazeutischen Praxis*, 5th ed., Vol. 4, Berlin, Springer-Verlag, 1992:839–848.
90. Chevallier A. *Encyclopedia of herbal medicine*. New York, DK Publishing, 2000.

Folium cum Flore Crataegi*

Definition

Folium cum Flore Crataegi consists of the dried flower-bearing branches of *Crataegus monogyna* Jacq. (Lindm), *C. laevigata* (Poir.) DC, their hybrids or, more rarely, other *Crataegus* species (Rosaceae).[1]

Synonyms

Crataegus monogyna Jacq. (Lindm): *C. apiifolia* Medik. non Michx., *C. Oxyacantha* L. ssp. *monogyna* Lev., *Mespilus elegans* Poir., *M. monogyna* All., *M. Monogyna* Ehrh. (*3*).

Crataegus laevigata (Poir.) DC: *C. oxyacantha* L., *C. oxyacantha* L. ssp. *Polygala* Lev., *C. oxyacanthoides* Thuill, *Mespilus oxyacantha* (Gartn.) Crantz. (*1*, *3*, *4*).

Selected vernacular names

Aubeline, aubepine, biancospino, calabrice, calavrice, eenarijlige meidorn, eenstijlige meidorn, eingriffeliger Weissdorn, Einkern-Weissdorn, épine blanche, espinero, espino blanco, espino majuelo, galagonya virágzó ágvég, hagdorn, hagedorn, harthorne, haw, hawthorn, hedge thorn, majuelo, may, May thorn, Mehlbeerbaum, Mehldorn, seiyosanzashi, shanzha, sorkh valik, spina, Stumpf gelappter Weissdorn, Weissdorn, whitethorn, za bur, zu'rurr el awdiyah, zweigriffeliger Weissdorn, Zweikern-Weissdorn (*1*, *3*, *5–8*).

Geographical distribution

Common to the temperate areas of the northern hemisphere, including eastern areas of North America, parts of South America, east Asia and Europe (*9*, *10*).

---

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

[1] Fructus Crataegi is included in the European pharmacopoeia (1) and in the pharmacopoeia of the People's Republic of China (2). However, clinical and pharmacological data for this plant part are insufficient to justify monographing at this time.

Description

Crataegus monogyna: a thorny shrub; leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of *C. laevigata*. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, stamen with black anthers and 1 style (*1*, *9*).

Crataegus laevigata: a thorny shrub; twigs glabrescent, brown; leaves bright green, obovate, with 3, 5 or 7 shallow, obtuse lobes. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles; fruits deep red, globose or ellipsoid (*9*, *11*).

Plant material of interest: dried leaf with flower

General appearance

Crataegus monogyna: leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of *C. laevigata*, with secondary venation curved outwards. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, anthers black with 1 style; sepals lanceolate, acuminate, falling over the ovary after flowering (*1*, *9*).

Crataegus laevigata: leaves bright green with 3, 5 or 7 shallow, obtuse, converging lobes, with secondary venation curved inward. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles.

Organoleptic properties

Odour: characteristic, faint; taste: slightly bitter-sweet, astringent (*12–15*).

Microscopic characteristics

Leaf dorsoventral; cells of upper epidermis polygonal, straight-walled with striated cuticle, those of lower epidermis more sinuous; anomocytic stomata on lower epidermis only; covering trichomes on both epidermises but more numerous on the lower, which are long, tapering, unicellular or very occasionally uniseriate with 2 cells, walls moderately thickened; cluster crystals or groups of small prismatic crystals of calcium oxalate in

the cells along the veins. Epidermis of floral pedicel and receptacle contain abundant covering trichomes similar to those on the leaf, but longer and more undulating; calyx with numerous anomocytic stomata on the outer epidermis, inner epidermis with a striated cuticle; epidermal cells of corolla distinctly papillose; fibrous layer of anther with characteristic thickenings; pollen grains spherical to elliptical, up to 45 µm in diameter, with 3 germinal pores and faintly granular exine. Epidermal cells of stem have thickened anticlinal outer walls; cortex parenchymatous with prismatic and cluster crystals of calcium oxalate; dense groups of small, tightly packed pericyclic fibres with much thickened and lignified walls; xylem completely lignified, composed of scattered vessels, thick-walled fibres and parenchyma separated by distinct medullary rays containing brown-coloured matter; larger vessels with bordered pits, smaller elements with annular or spiral thickening; central pith parenchymatous and lignified, cells with moderately thickened walls and numerous pits (*12*, *15*).

Powdered plant material

Yellowish-green. Unicellular covering trichomes, usually with a thick wall and wide lumen, almost straight or slightly curved, pitted at the base; fragments of leaf epidermis with cells which have sinuous to polygonal anticlinal walls and large anomocytic stomata surrounded by 4–7 subsidiary cells; parenchymatous cells of mesophyll containing cluster crystals of calcium oxalate, usually 10–20 µm in diameter; cells associated with veins contain groups of small prismatic crystals. Petal fragments showing rounded polygonal epidermal cells, strongly papillose, thick walls with clearly visible wavy striations in the cuticle; anther fragments showing endothecium with an arched and regularly thickened margin. Stem fragments containing collenchymatous cells, bordered, pitted vessels and groups of lignified sclerenchymatous fibres with narrow lumina. Numerous spherical to elliptical or triangular pollen grains up to 45 µm in diameter, with 3 germinal pores and a faintly granular exine (*1*).

General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography (*1*, *7*), and microchemical test for the presence of procyanidins (*7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Foreign organic matter

Not more than 8% lignified branches with a diameter greater than 2.5 mm (*1*) and not more than 2% other foreign matter (*1*, *15*).

Total ash

Not more than 10% (*1*).

Loss on drying

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*17*). For other pesticides, see the *European pharmacopoeia* (*17*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*18*).

Other purity tests

Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

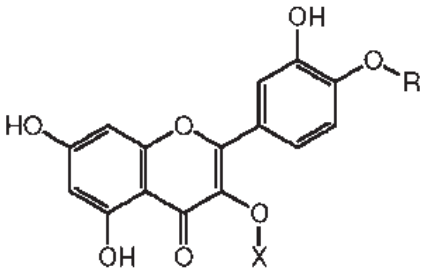
Chemical assays

Contains not less than 1.5% of flavonoids, calculated as hyperoside (*1*), and not less than 0.6% of flavone C-glycosides, calculated as vitexin (*14*), determined by spectrophotometry at 410 and 336 nm, respectively (*1*). A high-performance liquid chromatography method is also available (*19*).

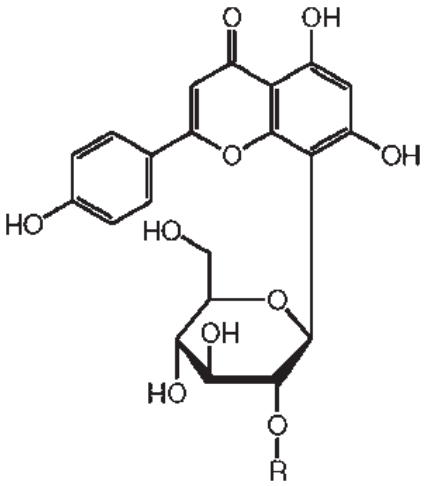
Major chemical constituents

The major constituents are flavonoids (rutin, hyperoside, vitexin, vitexin-2˝ rhamnoside, acetylvitexin-2˝ rhamnoside) and related proanthocyanidins (*19*, *20*). In the inflorescence, flavonol glycosides, mainly in the form of hyperoside, spiraeoside and rutin, are present. The primary flavo-

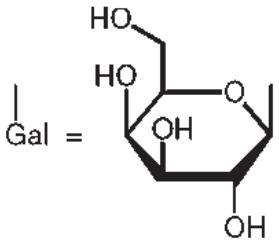
noid derivatives in the leaves are *epi*-catechin (*epi*-catechol) and/or catechin (catechol), and the related procyanidins formed during condensation of 2–8 monomeric units of the above catechins (*19*–*22*), together with oligomeric procyanidins (*23*). The presence of simple phenolic acids (e.g. chlorogenic and caffeic acids) has also been reported. Of the non-phenolic constituents, pentacyclic triterpenes (e.g. ursolic and oleanolic acids) and the 2-α-hydroxy derivative of oleanolic acid, known as crataegolic acid, are among the characteristic components (*4*). The structures of the characteristic constituents are presented below.



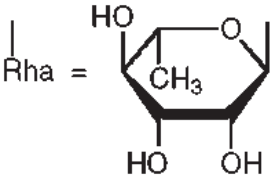
	R	X
hyperoside	H	Gal
spiraeoside	Glc	H
rutin	H	Rha-Glc



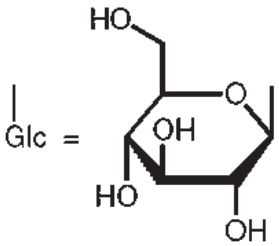
vitexin R = H
vitexin 2″-rhamnoside R = Rha



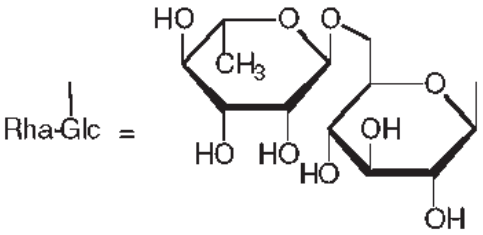
β-D-galactopyranosyl



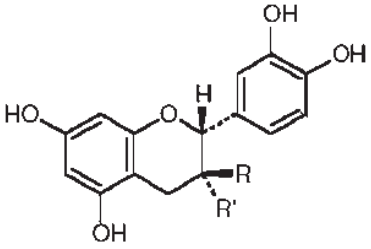
α-L-rhamnopyranosyl = 6-deoxy-α-L-mannopyranosyl



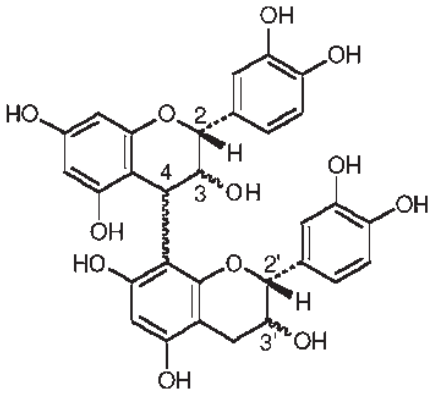
β-D-glucopyranosyl



6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl



	R	R'
catechin (catechol)	OH	H
epi-catechin (*epi*-catechol)	H	OH



procyanidin	2	2'	3	3'	4
B_1	α-(*R*)	α-(*R*)	α-(*R*)	β-(*S*)	β-(*R*)
B_2	α-(*R*)	α-(*R*)	α-(*R*)	α-(*R*)	β-(*R*)
B_3	α-(*R*)	α-(*R*)	β-(*S*)	β-(*S*)	α-(*S*)
B_4	α-(*R*)	α-(*R*)	β-(*S*)	α-(*R*)	α-(*S*)

Medicinal uses

Uses supported by clinical data

Treatment of chronic congestive heart failure stage II, as defined by the New York Heart Association (*24–34*).

Uses described in pharmacopoeias and in traditional systems of medicine

Support of cardiac and circulatory functions (*35*).

Uses described in folk medicine, not supported by experimental or clinical data

As an antispasmodic agent in the treatment of asthma, diarrhoea, gall bladder disease and uterine contractions, and as a sedative for the treatment of insomnia (*5*).

Pharmacology

Experimental pharmacology

Inotropic effects

Positive inotropic effects of Folium cum Flore Crataegi and its constituents have been demonstrated both in vitro and in vivo. These effects are

generally attributed to the flavonoid and procyanidin constituents of the leaves with flowers (*3*, *36–38*). A hydroalcoholic extract of the flowers with leaves, flavonoid and procyanidin fractions of the extract, and isolated constituents (e.g. biogenic amines, crataegolic acid, *epi*-catechin, hyperoside, luteolin 7-glucoside, rutin and vitexin) all have positive inotropic effects, and prolong the refractory period in cardiac myocytes, isolated papillary muscles and isolated guinea-pig hearts (*36–48*). In isolated guinea-pig hearts perfused at constant pressure, 3 µg/ml of a standardized extract increased the contractility of the heart by 9.5% (*40*). In isolated, electrically stimulated strips of failing human left ventricular myocardium, a standardized extract (18.75% oligomeric procyanidins) increased the force of contraction at concentrations higher than 10 µg/ml; a 100 µg/ml extract improved the force–frequency relationship (*39*). A standardized extract of the leaves and flowers increased the contractility of myocardial cells by 153%, at a concentration of 120 µg/ml (*44*). An aqueous extract of the leaves with flowers, two proanthocyanidin fractions and two flavonoid fractions of the extract dilated coronary blood vessels, and had positive inotropic effects on isolated guinea-pig hearts (extract or fraction: 0.05 mg/ml) (*41*).

Chronotropic effects

Intragastric administration of a macerate or fluidextract of the shoots, flowers or leaves to rats (12.5–25.0 mg/kg body weight) significantly inhibited arrhythmias induced by aconitine, calcium chloride or chloroform/epinephrine ($P < 0.05$) (*49*, *50*). The extracts also reduced blood pressure in rats at the same dosage (*49*, *50*). Aconitine-induced arrythmias were also inhibited after intravenous administration of a 95% ethanol extract of the bark and leaves (50 mg/kg body weight) to rabbits (*51*). Intravenous administration of a flavonoid-enriched extract of the leaves and flowers to rabbits (20 mg/kg body weight) or rats (2 mg/kg body weight) inhibited barium chloride-induced arrhythmias (*52*, *53*). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized dogs (7.5–30.0 mg/kg body weight) increased maximum left ventricular contraction velocity by 16.8–31.1% (*54*).

An aqueous extract improved cardiac performance during reperfusion, reduced lactate levels and accelerated energy metabolism in reperfused ischaemic rat heart. No increase in coronary blood flow was observed (*55*). Intragastric administration of single doses of a standardized extract (containing 18.75% oligomeric procyanidins) of the leaves with flowers (100 mg/kg body weight) or an oligomeric procyanidin-enriched fraction (20 mg/kg body weight) daily to rats protected against perfusion-induced

arrhythmias, hypotensive crisis and mortality (*56*, *57*). The oligomeric procyanidin-enriched fraction did not decrease the reperfusion-induced elevation of creatine kinase plasma levels (*57*). Administration of powdered leaves and flowers to rats (2% of diet) reduced the release of lactate dehydrogenase after perfusion-induced heart ischaemia (*58*).

Effect on coronary blood flow

Intragastric administration of an oligomeric procyanidin fraction of a standardized leaf and flower extract to dogs at a dose of 12–70 mg/kg body weight, three times daily for 60 days, increased myocardial blood flow (*59*, *60*). Intravenous injection of an aqueous or 95% ethanol extract of the flowers increased coronary blood flow and cardiac output, and decreased peripheral resistance in both dogs and guinea-pigs (*61–63*). Administration of a flavonoid-enriched extract to cats and rabbits increased coronary blood flow by 48% and 163%, respectively, and reduced pituitrin-induced coronary insufficiency in rabbits (*52*). Intravenous administration of a leaf with flower extract to cats (10 mg/kg body weight) or rabbits (20 mg/kg body weight) dilated coronary blood vessels, and improved coronary blood flow (*53*).

Effect on action potential

A leaf preparation (10 mg/l) prolonged the duration of the action potential and delayed the recovery of V_{max} in isolated guinea-pig papillary muscle (*42*). The electrophysiological correlation between the increase in the contraction amplitude of isolated canine papillary muscles, and vasodilation in isolated human coronary arteries, was measured after application of an extract of the leaves with flowers. The cardiac action potential significantly increased in duration and overshoot, and maximal depolarization ($P < 0.001$). Hyperpolarization of the resting membrane of normal and arteriosclerotic vascular smooth muscle cells of the human coronary artery was observed after treatment with flavonoids isolated from the extract (0.1 and 100 µmol/l). The isometric wall tension decreased in both normal and arteriosclerotic vessels. The increase of peak-to-plateau repolarization in cardiac action potential and hyperpolarization of vascular smooth muscle suggest that the extract acts as a potassium channel agonist (*64*, *65*).

Antihypertensive effects

In various animal models, a decrease in peripheral vascular resistance and hypertension occurred after treatment with leaf and/or flower extracts (*50*, *54*, *66–69*). Intravenous administration of a standardized fluidextract of the

leaves with flowers (equivalent to 6 mg of procyanidins/kg body weight) to anaesthetized normotensive dogs decreased norepinephrine-induced elevation of blood pressure. The extract (equivalent to 0.03 mg procyanidins/ml) also had β-blocking activity and inhibited epinephrine-induced tachycardia in isolated frog hearts (*69*). Hyperoside, isolated from an extract of the leaves and flowers, administered either intravenously at a dose of 1 mg/kg body weight or by infusion at 0.1 mg/kg body weight/min for 30 min, decreased blood pressure in anaesthetized dogs (*68*). Intravenous administration of an aqueous extract of the leaves (average dose 31 mg/kg body weight) decreased the systolic, diastolic and mean blood pressure in normotensive anaesthetized rats (*66*). Acute or chronic intragastric administration of a fluidextract or a glycerol/ethanol extract reduced arterial blood pressure in normotensive rats and in rats with desoxycorticosterone acetate-induced hypertension (*50*). Intragastric administration of a standardized extract (300 mg/kg body weight daily) decreased blood pressure by 9 mm Hg (1.20 kPa) (*67*). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized rats (30 mg/kg body weight) or dogs (15 mg/kg body weight) decreased total peripheral resistance and arterial blood pressure (*54*).

Anti-inflammatory effects

Both free radical production and lipid peroxidation are involved in various pathological processes, including cardiac ischaemia. As determined by in vitro studies, Folium cum Flore Crataegi has free radical scavenging and antioxidant activities. A standardized extract (containing 18.75% oligomeric procyanidins) and an oligomeric procyanidin-fraction of the extract inhibited lipid peroxidation (IC_{50} 0.48 µg/ml (extract), 0.3 µg/ml (fraction)), and the activity of human neutrophil elastase (IC_{50} 4.75 µg/ml (extract), 0.84 µg/ml (fraction)) (*56*). A 70% methanol extract of the flower buds inhibited lipid peroxidation in rat liver microsomes (IC_{50} 23 µg/l) (*70*, *71*). Both phenolic and flavonoid-enriched fractions of extracts of the leaves and flowers had antioxidant activity in vitro (*70–72*).

Effect on signal transduction

An aqueous or methanol extract of the leaves with flowers, as well as hyperoside, vitexin and vitexin rhamnoside, inhibited the activity of cyclic AMP-dependent phosphodiesterase isolated from guinea-pig or rat heart (*73*, *74*). Both luteolin 7-glucoside and rutin were also active (*75*). Hydroalcoholic extracts of the flowers and flower heads inhibited the formation of thromboxane A_2 and prostaglandin I_2 in rabbit cardiac tissues in vitro, thus indicating an anti-inflammatory effect of the extracts (*76*, *77*). A standardized ex-

tract (containing 18.75% oligomeric procyanidins) displaced ^{3}H-ouabain bound to sodium- and potassium-activated adenosine triphosphatase (*39*).

Anticontractile effects

An aqueous extract of the flowers inhibited barium chloride-induced contractions in rabbit intestine in vitro (*78*). A flavonoid-enriched extract of the leaves with flowers inhibited both histamine- and nicotine-induced contractions in rabbit intestine in vitro and partially inhibited contractions induced by barium chloride, acetylcholine or serotonin (ED_{50} 0.02 mg/ml) (*52*). Intravenous administration of a flavonoid-enriched extract of the leaves with flowers to cats (20 mg/kg body weight) inhibited contractions in intestinal smooth muscle, and intraperitoneal injection (400 mg/kg body weight) inhibited acetic acid-induced writhing in mice (*52*).

Sedative effects

Sedative effects have been observed in various animal models after intragastric administration of leaf with flower extracts (*79*, *80*). A 60% ethanol extract of the flowers increased hexobarbital-induced sleeping times, and decreased spontaneous motility and exploratory behaviour in female mice (800 mg/kg body weight) (*80*).

Diuretic effects

A flavonoid-enriched fraction of a flower extract had diuretic activity in dogs (50 mg/kg body weight) (*81*).

Toxicology

Single-dose toxicity studies have demonstrated that rats and mice tolerate 3 g/kg body weight, by gastric lavage, of a standardized hydroalcoholic extract of the leaves with flowers (containing 18.75% oligomeric procyanidins) without any clinical symptoms of toxicity. The intraperitoneal median lethal dose (LD_{50}) was 1.17 g/kg body weight in rats and 750 mg/kg body weight in mice. No toxic effects were observed in a repeat-dose toxicity study in which rats and dogs were given a standardized extract (containing 18.75% oligomeric procyanidins) at doses of 30, 90 and 300 mg/kg body weight daily by the intragastric route for 26 weeks (*82*).

Clinical pharmacology

Cardiac insufficiency

Review of the pharmacological and clinical data indicates that standardized extracts of Folium cum Flore Crataegi increase myocardial performance, improve myocardial circulatory perfusion and tolerance in cases of

oxygen deficiency, have antiarrhythmic effects and reduce afterload (*29*). Positive therapeutic effects of Folium cum Flore Crataegi in patients with characteristic symptoms of an activated sympathoadrenergic system, such as hypertension, tachycardia and arrhythmia (also characteristic of cardiac insufficiency stage II, as defined by the New York Heart Association (*25–34*)), have also been demonstrated (*30*). Furthermore, numerous clinical trials with and without controls have assessed the therapeutic efficacy of Folium cum Flore Crataegi extracts for the treatment of cardiac insufficiency stage II (*25–34*). The investigations were performed with a dried 70% methanol or 45% ethanol standardized extract (containing 2.2% flavonoids or 18.75% oligomeric procyanidins, respectively) of the leaves with flowers (*30*). The dosage ranged from 160 to 900 mg extract daily for 4–8 weeks. Evaluation of efficacy of the extracts was based on the following criteria: anaerobic threshold (*27*); Clinical Global Impression Scale (*31*, *32*); exercise tolerance (*25*, *26*, *28*, *31*, *32*, *34*); ventricular ejection fraction (*26*, *33*); quality of life and improvement of subjective symptoms (defined by the New York Heart Association) (*26–28*, *31–34*) and pressure/rate product (*26*, *28*, *31*, *32*, *34*). Although improvements were seen, no long-term trials have assessed the effects of Folium Cum Flore Crataegi on mortality rates in patients with chronic congestive heart failure.

Exercise tolerance

A randomized, double-blind, placebo-controlled trial assessed the efficacy of the extract containing 2.2% flavonoids on exercise-induced anaerobic threshold, as measured by spiroergometry, in 72 patients. Patients were administered an oral dose of 900 mg extract or placebo daily for 8 weeks. After treatment, oxygen uptake increased significantly in the treated group ($P < 0.05$), and exercise time to anaerobic threshold increased by 30 seconds in the treated group, but by only 2 seconds in the placebo group. Significant improvements in subjective symptoms were also noted in the treated group, as compared with the placebo group ($P < 0.01$) (*27*).

The efficacy of the extract containing 2.2% flavonoids on the improvement of exercise tolerance was assessed by bicycle ergometry in patients with cardiac insufficiency stage II, in three clinical trials. In a double-blind, placebo-controlled trial of 85 patients, oral administration of 300 mg extract daily for 4–8 weeks improved working capacity; however, the difference was not significant when compared with the placebo (*25*). A double-blind, placebo-controlled trial assessed the efficacy of oral administration of 600 mg extract daily for 8 weeks in 78 patients. Patients in the treatment group had a significant improvement in exercise tolerance as compared with the placebo group ($P < 0.001$). Patients who received the

extract also had lower blood pressure and heart rate during exercise, and had fewer overall symptoms, such as dyspnoea and fatigue (*31*). In the third trial, 132 patients were treated orally with 900 mg extract or 37.5 mg captopril daily for 8 weeks in a double-blind comparative study. Exercise tolerance, measured after 56 days of treatment, improved significantly in both groups ($P < 0.001$). In addition, the pressure/rate product was reduced, and the incidence and severity of symptoms such as dyspnoea and fatigue decreased by approximately 50% (*32*).

Pressure/rate product

Two double-blind, placebo-controlled trials assessed the efficacy of the extract containing 18.75% oligomeric procyanidins in a total of 156 patients with stage II cardiac insufficiency. Patients were treated orally with 160 mg extract or placebo daily for 8 weeks. The main parameters measured were the pressure/rate product using a bicycle ergometer, and the score of subjective symptom status. Patients treated with the extract exhibited a significant improvement in exercise tolerance, as compared with the placebo group ($P < 0.05$), and also a decrease in subjective complaints (*28*, *34*). In addition, a slight reduction in the systolic and diastolic blood pressure was noted in both groups (*28*).

Ventricular ejection fraction

In a trial without controls involving seven patients with stages II and III cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, oral administration of 240 mg extract containing 18.75% oligomeric procyanidins daily for 4 weeks increased the ventricular ejection fraction from 29.80 to 40.45%, as measured by angiography. Symptomatic complaints (Complaint List as defined by von Zerssen) also showed improvements (*33*). The effects of the extract containing 18.75% oligomeric procyanidins on haemodynamics were also investigated by radionuclide angiocardiography in a study without controls. Twenty patients with stage II cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, were treated with 480 mg extract. After treatment, the ejection fraction increased from 40.18 to 43.50% at rest, and from 41.51 to 46.56% under exercise conditions. Ergometric tolerance to exercise improved, blood pressure decreased and subjective complaints were reduced (*26*).

Pharmacokinetics

Absorption of a ^{14}C-labelled oligomeric procyanidin fraction of standardized extracts of leaves with flowers was measured in mice after intragas-

tric administration (0.6 mg). The results demonstrated that 20–30% of the total fraction, 40–81% of the trimeric procyanidins and 16–42% of the oligomeric procyanidins were absorbed within 1–7 hours after administration. After 7 hours, 0.6% of the radioactivity of the total fraction was eliminated by expiration and 6.4% was eliminated in the urine. Daily intragastric administration of 0.6 mg of a radiolabelled oligomeric procyanidin fraction to mice for 7 days led to an accumulation of radioactivity that was 2–3 times that in mice given a single dose (*83*).

Contraindications

None (*84*).

Warnings

Accurate diagnosis of stage II congestive heart failure should be obtained prior to use of Folium cum Flore Crataegi. Consult a physician if symptoms worsen, remain unchanged for longer than 6 weeks, or if water accumulates in the legs. Medical attention is absolutely necessary if pain occurs in the region of the heart, spreading out to the arms, upper abdomen or neck area, or in cases of respiratory distress (e.g. dyspnoea) (*84*).

Precautions

Drug interactions

None (*84*).

Drug and laboratory test interactions

No effects in laboratory tests (i.e. serum levels of sodium chloride, potassium chloride, calcium chloride, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, γ-glutamyl transpeptidase, total bilirubin, cholesterol and creatinin, and blood glucose levels) were observed (*34*).

Carcinogenesis, mutagenesis, impairment of fertility

A standardized extract of Folium cum Flore Crataegi (containing 18.75% oligomeric procyanidins) was not mutagenic or clastogenic in the *Salmonella*/microsome assay, mouse lymphoma test, cytogenetic analysis in cultured human lymphocytes or in the mouse bone marrow micronucleus test (*82*). A fluidextract was moderately active in the *Salmonella*/microsome assay in *S. typhimurium* strain TA98 only after

metabolic activation. The mutagenic activity appeared to be due to the quercetin content of the extract; however, the amount of quercetin ingested in a normal daily diet is higher than would be obtained from the extract (*85*). Intragastric administration of up to 1.6 g/kg body weight had no effect on the fertility of female and male rats or the F_1 generation (*86*).

Pregnancy: teratogenic effects

Intragastric administration of up to 1.6 g/kg body weight of a standardized extract of Folium cum Flore Crataegi to rats and rabbits was not teratogenic (*86*).

Pregnancy: non-teratogenic effects

No peri- or postnatal toxicity was observed in rats treated intragastrically with a standardized extract of Folium cum Flore Crataegi (1.6 g/kg body weight) (*86*).

Other precautions

No information available on general precautions or precautions concerning nursing mothers or paediatric use. Therefore, Folium cum Flore Crataegi should not be administered during lactation or to children without medical supervision.

Adverse reactions

None (*84*).

Dosage forms

Crude drug for infusion and hydroalcoholic extracts (*35*). Store in a well-closed container, protected from light and moisture (*1*).

Posology

(Unless otherwise indicated)

Daily dosage: 160–900 mg dried 45% ethanol or 70% methanol extract (drug:extract ratio 4–7:1) standardized to contain 18.75% oligomeric procyanidins (calculated as *epi*-catechin) or 2.2% flavonoids (calculated as hyperoside), respectively (*26–29*, *31–34*, *84*); 1.0–1.5 g comminuted crude drug as an infusion 3–4 times daily (*35*). Therapeutic effects may require 4–6 weeks of continuous therapy (*84*).

References

1. *European pharmacopoeia*, 3rd ed., Suppl. 2000. Strasbourg, Council of Europe, 1999.
2. *Pharmacopoeia of the People's Republic of China. Vol. I* (English ed.). Beijing, Chemical Industry Press, 1997.
3. Hänsel R et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Bd. 4: Drogen A-D*, 5th ed. Berlin, Springer-Verlag, 1994.
4. Steinegger E, Hänsel R. *Pharmakognosie*. Berlin, Springer-Verlag, 1996:580–584.
5. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
6. Newall CA, Anderson LA, Phillipson JD. *Herbal medicines, a guide for healthcare professionals*. London, Pharmaceutical Press, 1996.
7. *Pharmacopoeia Hungarica*, 7th ed. Budapest, Hungarian Pharmacopoeia Commission, Medicina Konyvkiado, 1986.
8. Ahumada C. The effects of a triterpene fraction isolated from *Crataegus monogyna* Jacq. on different acute inflammation models in rats and mice. Leucocyte migration and phospholipase A2 inhibition. *Journal of Pharmacy and Pharmacology*, 1997, 49:329–331.
9. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
10. Pizarro CM. *Sinopsis de la Flora Chilena*. Santiago, Ediciones de la Universidad de Chile, 1966.
11. Tutin TG, ed. *Flora Europea. Vol. 4*. Cambridge, Cambridge University Press, 1976.
12. *Deutsches Arzneibuch*. Stuttgart, Deutscher Apotheker Verlag, 1998.
13. *Pharmacopée française*. Paris, Adrapharm, 1996.
14. *Pharmacopoea helvetica*, 8th ed. Berne, Département fédéral de l'intérieur, 1997.
15. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
16. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
17. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
18. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
19. Rehwald A, Meier B, Sticher O. Qualitative and quantitative reversed-phase high-performance liquid chromatography of flavonoids in *Crataegus* leaves and flowers. *Journal of Chromatography A*, 1994, 677:25–33.
20. Krawczyk U, Pteri G, Kery A. HPLC analysis of procyanidins in *Crataegus* extract. *Archive der Pharmazie*, 1991, 324:97–99.

21. Ficarra P et al. High-performance liquid chromatography and diffuse reflectance spectroscopy of flavonoids in *Crataegus oxycantha* L. III. Analysis of 2-phenylchroman derivatives and caffeic acid. *Il Farmaco*, 1990, 45:237–255.
22. Kolodziej H, Ferreira D, Roux DG. Synthesis of condensed tannins. Part 12. Direct access to [4,6]- and [4,8]-all-2,3-*cis* procyanidin derivatives from (–)-epicathechin: assessment of bonding positions in oligomeric analogues from *Crataegus oxycantha* L. *Journal of the Chemical Society Perkin Transactions I*, 1984:343–350.
23. Thompson RS et al. Plant proanthocyanidins. Part 1. Introduction: the isolation, structure, and distribution in nature of plant procyanidins. *Journal of the Chemical Society Perkin Transactions I*, 1972:1387–1399.
24. American Heart Association Medical/Scientific Statement. 1994 revisions to classification of functional capacity and objective assessment of patients with heart diseases. *Circulation*, 1994, 90:644–645.
25. Bödigheimer K, Chase D. Wirksamkeit von Weissdorn-Extrakt in der Dosierung 3 × 100 mg täglich. Multizentrische Doppelblind-Studie mit 85 herzinsuffizienten Patienten im Stadium NYHA II. *Münchener Medizinische Wochenschrift*, 1994, 136 (Suppl. 1):18–21.
26. Eichstädt H et al. Crataegus-Extrakt hilft dem Patienten mit NYHA-II Herzinsuffizienz. Untersuchung der myokardialen und hämodynamischen Wirkung eines standardisierten Crataegus-Präparates mit Hilfe computergestützter Radionuklidventrikulographie. *Therapiewoche*, 1989, 39:3288–3296.
27. Förster A et al. Crataegus bei mässig reduzierter linksventrikulärer Auswurffraktion. *Münchener Medizinische Wochenschrift*, 1994, 136 (Suppl. 1):21–26.
28. Leuchtgens H. Crataegus-Spezialextrakt WS 1442 bei Herzinsuffizienz NYHA II. *Fortschritte der Medizin*, 1993, 111:352–354.
29. Loew D. *Crataegus*-Spezialextrakte bei Herzinsuffizienz. Gesicherte pharmakologische und klinische Ergebnisse. *Der Kassenarzt*, 1994, 15:43–52.
30. Loew D. Phytotherapy in heart failure. *Phytomedicine*, 1997, 4:267–271.
31. Schmidt U et al. Effect of hawthorne (*Crataegus*) preparation LI 132 in 78 patients with chronic congestive heart failure defined as NYHA functional class II. *Phytomedicine*, 1994, 1:17–24.
32. Tauchert M et al. Wirksamkeit des Weissdorn-Extraktes LI 132 im Vergleich mit Captopril. *Münchener Medizinische Wochenschrift*, 1994, 136 (Suppl. 1):27–33.
33. Weikl A, Noh HS. Der Einfluss von Crataegus bei globaler Herzinsuffizienz. *Herz und Gefässe*, 1992:516–524.
34. Weikl A et al. Crataegus-Spezialextrakt WS 1442. *Fortschritte der Medizin*, 1996, 114:291–296.
35. Wichtl M. Crataegi folium cum flore. In: Wichtl, M ed. *Teedrogen und Phytopharmaka*, 3rd ed. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1997:168–172.

36. Ammon HPT, Kaul R. *Crataegus*, Herz-Kreislauf-Wirkungen von Crataegusextrakten, Flavonoiden und Procyanidinen. Teil 1: Historisches und Wirkstoffe. *Deutsche Apotheker Zeitung*, 1994, 134:2433–2436.
37. Ammon HPT, Kaul R. *Crataegus*, Herz-Kreislauf-Wirkungen von Crataegusextrakten, Flavonoiden und Procyanidinen. Teil 2: Wirkungen auf das Herz. *Deutsche Apotheker Zeitung*, 1994, 134:2521–2535.
38. Ammon HPT, Kaul R. *Crataegus*, Herz-Kreislauf-Wirkungen von Crataegusextrakten, Flavonoiden und Procyanidinen. Teil 3: Wirkungen auf den Kreislauf. *Deutsche Apotheker Zeitung*, 1994, 134:2631–2636.
39. Brixius K et al. WS 1442 (*Crataegus*-Spezialextrakt) wirkt am insuffizienten menschlichen Myokard Kontraktionskraft-steigernd. *Herz Kreislauf*, 1998, 30:28–33.
40. Joseph G, Zhao Y, Klaus W. Comparative studies on the effect of *Crataegus* extract and different positive inotropic substances on the effective refractory period of ventricular myocardium. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 1995, 351:R103.
41. Leukel A et al. Studies on the activity of *Crataegus* compounds upon the isolated guinea-pig heart. *Planta Medica*, 1986, 53:545–546.
42. Müller A et al. Crataegus extract prolongs action potential duration in guinea-pig papillary muscle. *Phytomedicine*, 1996, 3:257–261.
43. Occhiuto F et al. Étude comparée de l'activité cardiovasculaire des jeunes pousses, des feuilles et des fleurs de *Crataegus oxyacantha* L. II. Action de préparations extractives et de principes actifs pur isolés sur le coeur isolés de lapin. *Plantes médicinales et Phytothérapie*, 1986, 20:52–63.
44. Pöpping S et al. Crataegus-Wirkung auf Kontraktion und O_2-Verbrauch isolierter Herzzellen. *Münchener Medizinische Wochenschrift*, 1994, 136 (Suppl. 1):39–46.
45. Pöpping S et al. Effect of a hawthorn extract on contraction and energy turnover of isolated rat cardiomyocytes. *Arzneimittel-Forschung*, 1995, 45:1157–1161.
46. Schüssler M et al. Effects of flavonoids from *Crataegus* species in Langendorff perfused isolated guinea pig hearts. *Planta Medica*, 1992, 58 (Suppl. 1):A646–A647.
47. Schüssler M et al. Myocardial effects of flavonoids from *Crataegus* species. *Arzneimittel-Forschung*, 1995, 45:842–845.
48. Wagner H, Grevel J. Herzwirksame Drogen IV; Kardiotone Amine aus *Crataegus oxyacantha*. *Planta Medica*, 1982, 45:98–101.
49. Costa R et al. Étude comparée de l'activité cardiovasculaire des jeunes pousses, des feuilles et des fleurs de *Crataegus oxyacantha* L. III. Action protectrice sur le coeur isolés de rat vis-à-vis des agents arythmogènes et dans les arythmies par reperfusions. *Plantes médicinales et Phytothérapie*, 1986, 20:115–128.
50. Occhiuto F et al. Étude comparée de l'activité cardiovasculaire des jeunes pousses, des feuilles et des fleurs de *Crataegus oxyacantha* L. I. Activité elec-

trique et tension arterielle chez le rat. *Plantes médicinales et Phytothérapie*, 1986, 20:37–51.
51. Thompson EB et al. Preliminary study of potential antiarrhythmic effects of *Crataegus monogyna*. *Journal of Pharmaceutical Sciences*, 1974, 63:1936–1937.
52. Manolov P, Nikolov KT. Crataemon experimental and clinical studies. *Bulletin Pharmachim*, 1969, 1:1.
53. Petkov V, Manolov P. Pharmacological studies on substances of plant origin with coronary dilating and antiarrhythmic action. *Comparative Medicine East and West*, 1978, 6:123–130.
54. Gabard B, Trunzler G. Zur Pharmakologie von *Crataegus*. In: Reitbrock N et al., eds. *Wandlungen in der Therapie der Herzinsuffizienz*. Braunschweig, Friedrich Vieweg und Sohn, 1983:43–53.
55. Nasa Y et al. Protective effect of *Crataegus* extract on the cardiac mechanical dysfunction in isolated perfused working rat heart. *Arzneimittel-Forschung*, 1993, 43:945–949.
56. Chatterjee SS et al. In vitro und in vivo-Untersuchungen zur kardioprotektiven Wirkung von oligomeren Procyanidinen in einem *Crataegus*-Extrakt aus Blättern mit Blüten. *Arzneimittel-Forschung*, 1997, 47:821–825.
57. Krzeminski T, Chatterjee SS. Ischemia and early reperfusion-induced arrhythmias: beneficial effects of an extract of *Crataegus oxyacantha* L. *Pharmacy and Pharmacological Letters*, 1993, 3:45–48.
58. Makdessi SA et al. Myocardial protection by pretreatment with *Crataegus oxyacantha*. An assessment by means of the release of lactate dehydrogenase by the ischemic and reperfused Langendorff heart. *Arzneimittel-Forschung*, 1996, 46:25–27.
59. Mävers WH, Hensel H. Veränderungen der lokalen Myokarddurchblutung nach oraler Gabe eines *Crataegus*-Extraktes bei nichtnarkotisierten Hunden. *Arzneimittel-Forschung*, 1974, 24:783–785.
60. Roddewig C, Hensel H. Reaktion der lokalen Myokarddurchblutung von wachen Hunden und narkotisierten Katzen auf orale und parenterale Applikation einer *Crataegus* Fraktion (oligomere Procyanidine). *Arzneimittel-Forschung*, 1977, 27:1407–1410.
61. Hockerts T, Mülke G. Beitrag zur Frage einer Coronarwirkung von wässrigen Extrakten aus *Crataegus*-Droge. *Arzneimittel-Forschung*, 1955, 5:755–757.
62. Jacobi H et al. Studies on the coronary effect of *Crataegus* extracts. *Arzneimittel-Forschung*, 1956, 6:98–99.
63. Kovach AGB et al. Effects of an extract from *Crataegus oxyacantha* on coronary blood flow in dogs. *Arzneimittel-Forschung*, 1958, 9:378–379.
64. Siegel G et al. Weissdorn-Extrakt LI 132. *Münchener Medizinische Wochenschrift*, 1994, 136 (Suppl. 1):47–56.
65. Siegel G et al. Molecular physiological effector mechanisms of hawthorn extract in cardiac papillary muscle and coronary vascular smooth muscle. *Phytotherapy Research*, 1996, 10 (Suppl. 1):S195–S198.

66. Abdul-Ghani AS et al. Hypotensive effect of *Crataegus oxyacantha. International Journal of Crude Drug Research*, 1987, 25:216–220.
67. Fehri B et al. *Valeriana officinalis* et *Crataegus oxyacantha* toxicité par administrations réitérées et investigations pharmacologiques. *Journale de Pharmacie de Belgique*, 1991, 46:165–176.
68. Liévre M et al. Étude des effets cardiovasculaires de l'hyperoside extrait de l'Aubépine chez le chien anesthésié. *Annales pharmaceutiques françaises*, 1985, 5:471–477.
69. Rácz-Kotilla E et al. Hypotensive and beta-blocking effect of procyanidins of *Crataegus monogyna. Planta Medica*, 1980, 39:239.
70. Bahorun T et al. Antioxidant activities of *Crataegus monogyna* extracts. *Planta Medica*, 1994, 60:323–328.
71. Bahorun T et al. Oxygen species scavenging activity of phenolic extracts from hawthorn fresh plant organs and pharmaceutical preparations. *Arzneimittel-Forschung*, 1996, 46:1086–1089.
72. Rakotoarison DA et al. Antioxidant activities of polyphenolic extracts from flowers, in vitro callus and cell suspension culture of *Crataegus monogyna. Pharmazie*, 1997, 52:60–64.
73. Petkov E et al. Inhibitory effect of some flavonoids and flavonoid mixtures on cyclic AMP phosphodiesterase activity of rat heart. *Planta Medica*, 1981, 43:183–186.
74. Schüssler M et al. Comparison of the flavonoids occurring in *Crataegus* species and inhibition of 3',5'-cyclic adenosine monophosphate phosphodiesterase. *Planta Medica*, 1991, 57 (Suppl. 2):A133.
75. Schüssler M et al. Cardiac effects of flavonoids from *Crataegus* species. *Planta Medica*, 1993, 59 (Suppl. 2):A688.
76. Vibes J et al. Inhibition of thromboxane A2 biosynthesis in vitro by the main components of *Crataegus oxyacantha* (hawthorn) flower heads. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 1994, 50:173–175.
77. Vibes J et al. Effects of a methanolic extract from *Crataegus oxyacantha* blossoms on TXA_2 and PGI_2 synthesising activities of cardiac tissue. *Medical Science Research*, 1993, 21:435–436.
78. Wrocinski T. Determination of the activity of spasmolytic drugs with reference to the papaverine standard. *Biuletyn Instytutu Roslin Leczniczych*, 1960, 6:236.
79. Beretz A et al. Choix de méthodes pharmacologiques pour l'étude des activités de l'aubépine. *Plantes médicinales et Phytothérapie*, 1978, 12:305–314.
80. Della Loggia R et al. Depressive effect of *Crataegus oxyacantha* L. on central nervous system in mice. *Science and Pharmacy*, 1983, 51:319–324.
81. Borkowski B. Diuretic action of several flavone drugs. *Planta Medica*, 1960, 8:95–104.
82. Schlegelmilch R, Heywood R. Toxicity of *Crataegus* (hawthorne) extract (WS 1442). *Journal of the American College of Toxicology*, 1994, 13:103–111.

83. Hecker-Niediek AE. *Untersuchungen zur Biogenese, Markierung und Pharmakokinetik der Procyanidine aus Crataegus-Species* [Dissertation]. Marburg, University of Marburg, 1983.
84. Blumenthal M et al., eds. *The complete German Commission E monographs.* Austin, TX, American Botanical Council, 1998.
85. Schimmer O et al. The mutagenic potencies of plant extracts containing quercetin in *Salmonella typhimurium* TA98 and TA100. *Mutation Research*, 1988, 206:201–208.
86. Albrecht A, Juretzek W. *Weissdorn* (*Crataegus laevigata, Crataegus monogyna*), *Weissdornblätter mit Blüten (Crataegi folium cum flore).* Berlin, Springer: Loseblatt System Naturheilverfahren, 1995.

Herba Equiseti

Definition

Herba Equiseti consists of the whole or cut, dried sterile aerial parts of *Equisetum arvense* L. (Equisetaceae) (*1*, *2*). The same parts collected during the summer are described in the *USSR pharmacopoeia* as Herba Equiseti arvensis (*2*).

Synonyms

E. calderi Boivin (*3*).

Selected vernacular names

Acker-schachtelhalm, acherschachtelhalm, ager-padderokke, åkersnelle, åkerfräken, akkerpaardestaart, at kuyrugi, baimbap, at quyroughi, bottlebrush, brusca, cauda de cavalo, chieh hsu ts'ao, coada calului, coda cavallina, coda equine, cola de caballo, common horsetail, corn horsetail, dhanab al khail, dhanab el khayl, dhanab et faras, dutch rushes, equiseto menor, equiseto dei boschi, equiseto dei campi, equisette, equisetto, erva carnuda, false horse-tail, field horsetail, foxtail, gongbangcho, heermoes, horse-pipe, horse pipes, horsetail, horsetail grass, horsetail rush, horse willow, hvoshtsh, jeinsol, jointed rush, kannenkraut, kattestaart, kilkah asb, klóelfting, koniogon, kosa tīruma, krypfräken, librus, macho, mare's tail, meadow pine, moeraspaardestaart, mokjeok, moonhyung, paddock-pipes, peltokorte, pest'shi, petite prêle, pewterwort, pildoochae, pildooy-eup, pine grass, pinetop, polevaja sosenka, prele, prêle des champs, põldosi, queue de cheval, queue de rat, queue de renard, rabo de cavalo, rasperella, rävrumpa, scouring rush, shvita, snake grass, soettgi, soksae, sugina, toadpipe, tolkatshnik, tomahwang, tsukushi, vara de oro, wen ching, western horsetail, zinngras, zinnkraut (*3–16*).

Geographical distribution

Distributed throughout the temperate zone of the northern hemisphere. Indigenous to all of America, Europe and North Africa, as well as parts of Asia**.** Found widely throughout the Newly Independent States region,

with the exception of deserts, *paramos* and the northern regions (*4*, *5*, *7*, *8*, *17–21*).

Description

A perennial plant with sterile and fertile stems. Rhizomes: horizontal, up to 3 mm in diameter, layered, extending to a depth of about 1 m, brownish-black, branched, creeping, with blackish tubers up to 7 mm in diameter. Roots: at the bases of lateral branch buds, on both rhizomes and erect shoots. Fertile stems: ephemeral, appear early in the spring, 15–20 cm high, up to 5 mm in diameter, unbranched, succulent, reddish or yellowish, jointed, with 6–12 blackish-brown lanceolate teeth at the joints. Cones: apical, ovate-cylindrical, blunt-tipped, 1–3.5 cm long. The strobile is situated under peltate polygons, which are pileus-like bodies, arranged in whorls; 4–7 spiral filaments surround the green globular spores, which roll up closely around them when moist, and uncoil when dry. The fertile stem never turns green. The green, sterile shoots develop later from the rhizome, by which time the fertile shoots have usually wilted. Sterile stems: 5–15(80) cm high, erect, 6–18(20) grooved, hollow, jointed, up to 20 whorls of slender branches. Leaves scale-like, deciduous, inconspicuous, in whorls at the nodes, are connected at their bases (*4*, *5*, *18*, *19*, *22–27*).

Plant material of interest: dried sterile aerial parts

General appearance

Whole sterile stems, 20–80 cm long (up to 30 cm long according to the *USSR pharmacopoeia* 1990 (*2*)), or fragments of 0.5–2 cm in length, and 3–5 mm in diameter, with 6–18(20) deep longitudinal grooves, light green to greenish-grey, rough to the touch, brittle and crunchy when crushed, hollow and jointed at the nodes, which occur at intervals of about 1.5–4.5 cm. Vaginas covering the stem nodes are cylindrical, 4–8 mm long, with teeth; the teeth are triangular-lanceolate, dark brown, with white-scaled margins, half as long as vagina, concrescent in groups of 2 or 3. Fracture short, exposing a large central cavity and the vascular canals of the cortex in the stems. Numerous solid branches arranged in whorls, pointing upwards, unbranched, 5–20 cm long, 1–2 mm in diameter, with 4–5 deep grooves. Leaf vaginas on the branches are cylindrical, green and have 4–5 teeth, which represent the extremely reduced leaves; the number of teeth corresponds to the number of grooves on the branches; the teeth are pale green or brownish, oblong-lanceolate, with acuminate apices; half or one third as long as vagina; connected between each other (*alter-*

nate) scales, forming a specific vaginate structure in the nodes of the branches, which is usually called a "sheath" (*1*, *2*, *28*, *29*).

Organoleptic properties

Odour: slight or no odour; taste: slightly acidic or no taste (*2*, *28*, *29*).

Microscopic characteristics

Epidermis with elongated, wavy-walled cells, silicified, often thickened and beaded. The paracytic stomata with the 2 subsidiary cells cover the guard cells and have conspicuous radial ridges. In transverse sectional view the epidermis is crenate, with the protuberances formed from the contiguous mass of 2 U-shaped cells. (No single-celled protuberances should be present – absence of *E. palustre L.*) The cortex of stems of thin-walled cells with many large lacunae; non-lignified, collenchymatous fibrous cells up to 1 mm long with oblique or bifurcate apices in the ridges; xylem of lignified, annularly or spirally thickened vessels occurring singly or in small groups; slightly lignified annularly thickened tracheids and bundles of long non-lignified fibres with narrow lumens. Large parenchymatous cells packed with minute starch grains; large central cavity. Branches have four vascular bundles and lack a central cavity; the silicified collenchyma is reduced, cortex lacunae are absent (*1*, *28–31*).

Powdered plant material

Greenish-grey or dull green. The powder shows characteristic elements of stems (see Microscopic characteristics) (*1*, *28*, *29*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the characteristic constituents: caffeic acid, hyperoside and rutin (*1*, *28*), quercetin 3-glucoside (*5*) and flavone-5-glucosides (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*32*).

Chemical

No information available.

Foreign organic matter
Maximum of 5% of stems from other *Equisetum* species and hybrids, and not more than 2% (*1*) or 1% of other foreign matter. For other parts of *Equisetum arvense* L., not more than 1% of other foreign matter and 4% of other *Equisetum* species (*2*). Blackish rhizome fragments and other foreign matter, not more than 5% (*33*).

Total ash
Minimum 12% and maximum 27% (*1*). Not more than 20% (*28*, *29*).

Acid-insoluble ash
Minimum 3%, maximum 15% (*1*). Not more than 10% (*28*, *29*).

Sulfated ash
No information available.

Water-soluble extractive
Not less than 15% (*28*, *29*).

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 10% (*1*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg. For other pesticides, see the *European pharmacopoeia* (*1*), the WHO guidelines on quality control methods for medicinal plants (*32*) and the WHO guidelines on pesticide residues (*34*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on control methods for medicinal plants (*32*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*32*) for the analysis of radioactive isotopes.

Other purity tests
No single-celled protuberances should be present (absence of *E. palustre* L.) (*28*, *29*). Not more than 2% foreign matter (*29*). Not more than

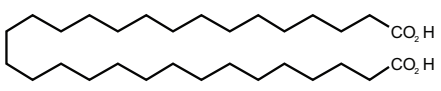
0.5% mineral matter (*2*). Thin-layer chromatography for determining the absence of other *Equisetum* species and hybrids (*1*, *30*). Chemical, sulfated ash and alcohol-soluble extractive limits to be established in accordance with national requirements.

Chemical assays

Contains not less than 0.3% of total flavonoids expressed as isoquercitroside (isoquercitrin) (*1*).

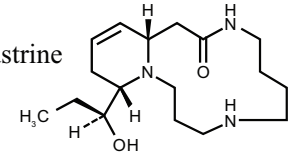
Major chemical constituents

Asian and North American varieties contain a large amount of quercetin 3-*O*-β-D-glucopyranoside (isoquercitrin) and its malonyl esters. Apigenin- and luteolin 5-*O*-glucosides, as well as their malonyl esters are also present. In the European chemotype, the flavonoids are mainly quercetin 3-*O*-sophoroside together with genkwanin and kaempferol derivatives, among them protogenkwanin 4´-*O*-β-D-glucopyranoside (*23*, *35*), genkwanin-5-*O*-glucoside, kaempferol 3,7-di-*O*-glucoside, kaempferol-3-*O*-(6´-*O*-malonyl-glucoside)-7-*O*-glucoside, kaempferol-3-*O*-sophoroside and glycosides of luteolin (among them the 5-glucopyranoside, galuteolin), onitin and onitin-9-*O*-glucoside (*4*, *36*, *37*). The plant also contains more than 10% inorganic constituents of which two thirds are silicates (which can constitute as much as 15% (*17*)) and potassium salts (*5*). Small amounts of gold (0.03–0.075 ppm) and silver (0.23 ppm) and lanthanides have been reported (*38*) as well as traces of alkaloids, including nicotine and spermidine-type bases, and palustrine. The sterols β-sitosterol, campesterol, isofucosterol and cholesterol are present (*37*). Other constituents reported include methoxypyridine, equisetonin, equisetroside, sapogenin and equisetogenin (*7*, *8*). In addition, there are saponins, carotenoids, polyenic acids, rare dicarboxylic acids (*5*) and organic acids (aconitic, arabinonic, caffeic, citric, equisetolic, fumaric, gallic, gluconic, glyceric, malic, malonic, protocatechuic and quinic), and rhodoxanthin, threonic, *p*-coumaric, 4-hydroxybenzoic and vanillic acid among others (*7*, *8*, *37*, *39*). The structures of some characteristic constituents are presented below.



equisetolic acid

palustrine



Medicinal uses

Uses supported by clinical data

An open clinical trial has indicated a possible diuretic effect (*40*).

Uses described in pharmacopoeias and well-established documents

Used internally for kidney and bladder diseases, oedema and as an adjuvant in slimming diets (*41*). It is applied as irrigation therapy for infectious and inflammatory diseases of the genitourinary tract, and kidney stones (*12, 23*, *42*). Used externally as supportive treatment for slowhealing wounds (*43*).

Uses described in traditional medicine

Symptomatic treatment of chronic swelling of the legs, slow-healing sprains and fractures, irritable skin conditions, gout, rheumatism, arthritis, hepatitis, fractures, sore throat, dermatological problems and haemorrhoids (*44–47*). In folk medicine Herba Equiseti is used as an analgesic, antihypertensive, clotting agent, haemostatic, depurative, astringent, diuretic and anti-inflammatory (*48–50*). In Indian Ayurvedic medicine it is used for the treatment of inflammation or benign enlargement of the prostate gland, for urinary incontinence and for enuresis in children (*51*).

Pharmacology

Experimental pharmacology

Antinociceptive and anti-inflammatory activity

An aqueous-ethanol extract of the stems of *Equisetum arvense* at concentrations of 10, 25, 50 and 100 µg/g, administered intraperitoneally, reduced the writhing induced in mice by acetic acid (49, 57, 93 and 98%, respectively). The results of treatment with the extract were positive but less marked in the formalin and carrageenan paw oedema tests, but were negative in the hotplate test. The antinociceptive and anti-inflammatory effects of the extract are thus confirmed in chemical models of nociception in vivo (*52*).

Sedative and anticonvulsant effects

In an open-field test in rats, an aqueous-ethanol extract of the aerial parts of *Equisetum arvense*, at doses of 200 and 400 mg/kg body weight (bw), had anticonvulsant activity. The treatment enhanced the number of falls in the rota-rod test, reducing the time of permanence on the bar. An increase in barbiturate-induced sleeping time was also observed (46% and

74%, at the 200 and 400 mg/kg bw doses, respectively). The extract increased the pentylenetetrazole-induced convulsion latency, diminished the severity of convulsions, reduced the percentage of rats which developed convulsions (25% and 50% at the 200 and 400 mg/kg bw doses, respectively) and protected animals from death, thus confirming the anticonvulsant effect of the extract (*53*).

Antiurolithiasis activity

Intravenous infusion of a hot aqueous extract of the dried aerial parts (dose not stated) to female Wistar rats showed antiurolithiasis activity both in prevention and in treatment of kidney stone formation (*54*).

Antimicrobial activity

The antibacterial activities of 90–95% ethanol extracts of the dried aerial parts were assessed in vitro. At a concentration of 500 µg/disc, the extracts exhibited weak activity against *Bacillus subtilis* and *Streptococcus faecalis*, but were inactive against *Escherichia coli*, *Aerobacter aerogenes*, *Bacillus globifer*, *Bacillus mycoides*, *Proteus morganii*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Serratia marcescens* and *Streptococcus aureus* (*55*, *56*). A methanol extract of the dried leaves at a maximum inhibitory concentration >500 µg/ml was inactive against *Mycobacterium avium* and *Mycobacterium smegmatis* in a study using a broth culture method (*57*).

The disc diffusion method was also used for the evaluation of the antimicrobial activity of the essential oil from the stems of *Equisetum arvense* against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Aspergillus niger* and *Candida albicans*. A 1:10 dilution of the essential oil was shown to possess a broad spectrum of antimicrobial activity against all strains tested (*58*).

A dried extract of the fresh aerial parts was active against *Aspergillus flavus* in vitro (concentration not stated) (*59*). The antifungal activity of an aqueous-ethanol extract of dried stems (1:1), at a concentration of 500 g/ml/agar plate was assessed. The results showed that the extract was inactive against *Aspergillus fumigatus*, *Aspergillus niger, Botrytis cinerea*, *Penicillium digitatum*, *Rhizopus nigricans*, *Trichophyton mentagrophytes*, *Candida albicans* and *Saccharomyces pastorianus* (*56*, *60*). A 95% ethanol extract at various concentrations was inactive against *Fusarium culmorum*, *Fusarium solani*, *Penicillium notatum* and *Scopulariopsis species* (*55*). An aqueous-methanol extract (1:1) of the dried aerial parts inhibited HIV-1 reverse transcriptase activity in cell culture at a concentration of 10% (*61*).

Antiplatelet activity

An aqueous extract of the dried aerial parts at a concentration of 1 mg/ml significantly inhibited collagen-, thrombin- and ADP-induced platelet aggregation in vitro (91.9%, $p < 0.001$). This antiaggregatory effect was dose-dependent (*62*, *63*).

Antioxidant, hepatoprotective and radical scavenging effects

An aqueous extract of the dried aerial parts (30 µl) exhibited radical scavenging effects in cultured lines of microsomes (*64*). The antioxidative activity of water and ethanol extracts of the aerial parts was investigated using different methods. The content of total phenolic components was higher in the ethanol extract, but the protein content was higher in the aqueous extract. The extracts had remarkable antioxidative activities, similar to those of 5 mM ascorbic acid. Water extracts showed high superoxide anion radical-scavenging activities. Hydroxyl radicals were effectively scavenged by ethanol extracts. The effects may be due to the presence of vitamins C and E, copper and zinc (*65*). Compounds isolated from the methanol extract of the plant (the phenolic petrosin onitin and flavonoid luteolin) exhibited hepatoprotective activities in vitro against tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, displaying median effective concentrations (EC_{50}) values of 85.8 ± 9.3 µM and 20.2 ± 1.4 µM, respectively. Silybin, used as a positive control, showed an EC_{50} value of 69.0 ± 3.3 µM. The isolated compounds also showed superoxide scavenging effects (IC_{50}, 35.3 ± 0.2 µM and 5.9 ± 0.3 µM, respectively) and 1,1-diphenyl-2-picrylhydrazyl-2,2-di(4-tert-octylphenyl)–1–picrylhydrazyl free radical scavenging effect (IC_{50}, 35.8 ± 0.4 µM and 22.7 ± 2.8 µM, respectively) (*36*).

Uterine stimulant activity

A weak in vitro uterine stimulant effect of a methanol extract of the aerial parts was observed using isolated uterus (unspecified condition) preparations from female rats at a dose of 5 mg/ml (*66*).

Toxicology

A methanol extract of the plant at a median effective dose of 20 µg/ml had a cytotoxic effect in a human leukaemia cell line (L1210) (*67*). A 10% aqueous extract and a methanol extract at a concentration of 50 µg/ml showed no cytotoxic activity in either HeLa or 9KB cell cultures (*68*, *69*). Oral administration of the dried entire plant (in rations) at variable concentrations (20% or more) caused an acute vitamin B_1 deficiency (antithiamine activity) in horses within 2–5 weeks, an effect known as equisetosis (*38*, *70*).

Clinical pharmacology

In an open uncontrolled clinical trial, sap from the aerial parts of Herba Equiseti, at a dose of one tablespoon (15 g) three times a day, was tested in patients with cardiac failure and oedema. All patients showed an augmentation of diuresis. In the same study, an infusion of 15 g of the plant in 180 ml of water was given in divided doses (one tablespoon every 2 hours) to a group of patients with oedema. Again, an increase in diuresis was observed in more than 50% of patients (*40*).

Adverse reactions

A cholesterol-rich diet (0.5% cholesterol and 0.15% sodium cholate for 14 days), to which 4% of Herba Equiseti powder had been added, caused dermatitis of the neck, head and back in 65% of rats. The effect was not observed when the rats were fed on a normal diet (*71*).

Contraindications

No irrigation therapy (hydrocolon therapy) is recommended in patients with oedema due to impaired heart and kidney function (*40*). If signs of hypersensitivity reactions appear, Herba Equiseti must not be used again.

Warnings

Ingestion of large amounts of Herba Equiseti is not recommended in combination with a cholesterol-rich diet (*72*).

Precautions

General

Care is necessary in the presence of diseases associated with serious renal lesions and inflammation (nephritis, nephrosis) due to the irritant action of Herba Equiseti (*73*, *74*). Do not use Herba Equiseti for more than 6 weeks except under professional supervision, as it may cause irritation of the digestive tract (*43*). A physician should be consulted when the drug is used as a bath additive in cases of major skin lesions, acute skin lesions of unknown origin, major feverish and infectious diseases, cardiac insufficiency or hypertension (*12*). If symptoms worsen or persist for longer than 5 days or in case of increased body temperature or presence of blood in urine, a physician should be consulted.

Drug interactions

No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
Because of the uterine stimulant activity (See Pharmacology) the herbal substance and its herbal preparations should not be used during pregnancy.

Nursing mothers
The herbal substance and its herbal preparations should not be used by nursing mothers.

Paediatric use
The herb in its powdered form is not recommended for children due to the inorganic silica content. Toxicity of the herb was found to be similar to nicotine poisoning in children who chewed the stems (*38*).

Dosage forms
Cut herb for infusions, decoctions and other equivalent Galenical preparations.

Posology
(Unless otherwise indicated)
For internal use. Average daily dose 6 g of herb as a decoction or infusion (1:5) given in divided doses three times daily (*75*). Fluid ethanol extract: 1:1 (g/ml), half a teaspoon (2 ml) 2 times daily (*76*). Tincture: 1:5 (g/ml), 10 ml three times daily.
For external use. To prepare a decoction for use in making a cataplasm or compress: add 10 g of herb to 1 l of boiling water for direct application to the skin (*23*). As a bath additive: add 2 g of herb to 1 l of hot water and steep for 1 hour, then add it to water in the bath (*51*).

References
1. *European pharmacopoeia*, 5th ed. Strasbourg, European Directorate for the Quality of Medicines, 2005.
2. *USSR pharmacopoeia*, 11th ed. *Vol. 2*. Moscow, Meditsina, 1990 [in Russian].
3. *Plants for a future*: *database search* (http://www.ibiblio.org/pfaf/D_search.html).
4. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific Publishers, 2001.

5. Bisset NG, Wichtl M. *Herbal drugs and phytopharmaceuticals: A handbook for practice on a scientific basis.* Stuttgart, Medpharm Scientific, 1994.
6. Turova AD, Sapozhnikova EN. *Lekarstvenn'je rastenija SSSR I ikh primenenije.* Moscow, Meditsina, 1982.
7. Han DR et al. *Modern pharmacognosy*. Seoul, Hakchang, 1988.
8. Kim IH et al. *Medicinal botany*. Seoul, Hakchang, 1988.
9. *Horsetail: Equisetum arvense L.* (http://user.chollian.net/~k95092/doc/s-sueddeugi.html).
10. Bedevian AK. *Illustrated polyglottic dictionary of plant names*. Cairo, Medbouly Library, 1994.
11. Zahedi E. *Botanical dictionary of scientific names of plants in English*, *French*, *German*, *Arabic and Persian languages.* Tehran, Tehran University Press, 1959.
12. *Physician's desk reference for herbal medicines.* Montvale, NJ Medical Economics Company, 2000.
13. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsiniereba, 1991.
14. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
15. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
16. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina*, *eesti*, *inglise*, *soome*, *vene*. Tartu, Celsius Healthcare, 2006.
17. Chevallier A. *Encyclopaedia of herbal medicine.* New York, DK Publishing, 2000.
18. Muravjova DA. *Farmakognozija.* Moscow, Meditsina, 1991.
19. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
20. Yakovlev GP, Blinova KF, eds. *Lekarstvennoje rastitel,noje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
21. Muravjova DA, R'batshuk IZ. *Farmakognozija*. Moscow, Meditsina, 1984.
22. Duke JA. *The green pharmacy.* Emmaus, PA, Rodale Press, 1997.
23. Blumenthal M et al., eds. *The complete German Commission E monographs. Therapeutic guide to herbal medicines.* Austin, TX, American Botanical Council, 1998.
24. Shishkin BK, Bobrov EG. *Flora SSSR. Vol. 15*. Pod red. Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1949.
25. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR. Izd.* Moscow, Mysli, 1976.
26. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR.* 3-ie izd. Kishinev, Shtiintsa, 1986.
27. *Botaniceskii atlas.* Moscow, Izdatel'stvo selskohozeaistvennoi literatury, jurnalov i plakatov, 1963.
28. *British herbal pharmacopoeia*. *Vol. 1*. Bournemouth, Scientific Committee of the British Medicine Association, 1990.

29. *British herbal pharmacopoeia*. Exeter, British Herbal Medicine Association, 1996.
30. Bruneton J. *Pharmacognosie*, *phytochimie*, *plantes medicinales,* 2nd ed. *Technique et documentation.* Paris, Lavoisier, 1993.
31. Abbayes H et al. *Botanique. Anatomie – Cycles évolutifs, Systématique*. Paris, Masson, 1963.
32. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
33. *Pharmacopoeia Helvetica*, 7th ed. Berne, Département Fédéral de l'Intérieur, 1987.
34. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
35. Veit M et al. Malonylated flavone 5-O-glucosides in the barren sprouts of *Equisetum arvense*. *Phytochemistry*, 1990, 29:2555–2560.
36. Oh H et al. Hepatoprotective and free radical scavenging activities of phenolic petrosins and flavonoids isolated from *Equisetum arvense. Journal of Ethnopharmacology*, 2004, 95:421–424.
37. *Rastitel'nye resursy.* Leningrad, Nauka, 1996.
38. Duke JA. *Handbook of medicinal herbs*, 2nd ed. Boca Raton, FL, CRC Press, 2002.
39. Takatsuto S, Abe H. Sterol composition of the strobilus of *Equisteum arvense* L. *Bioscience*, *Biotechnology and Biochemistry*, 1992, 56:834–835.
40. Petkov V, ed. *Sovremennaja fitoterapija.* Sofia, Meditsina i fizkultura, 1988.
41. Bruneton J. *Pharmacognosy*, *phytochemistry*, *medicinal plants*. Paris, Lavoisier, 1995.
42. Bradley PR, ed. *British herbal compendium*. *Vol. 1.* Bournemouth, British Herbal Medicine Association, 1992.
43. Chevallier A. *The encyclopaedia of medicinal plants*. London, Dorling Kindersley, 1996.
44. Knuth V. *Equisetum arvense*, the Bottle Brush. *Pharmazie*, 1947, 2:222–223.
45. Novaretti R, Lemordant D. Plants in the traditional medicine of the Ubaye valley. *Journal of Ethnopharmacology*, 1990, 30:1–34.
46. Owen P, Johns T. Xanthine oxidase inhibitory activity of northeastern North American plant remedies used for gout. *Journal of Ethnopharmacology*, 1999, 64:149–160.
47. Yarnell E. Botanical medicine for cystitis. *Alternative and Complementary Therapy*, 1997:269–275.
48. De Feo V, Senatore F. Medicinal plants and phytotherapy in the Amalfitan coast, Salerno. *Journal of Ethnopharmacology*, 1993, 1:39–51.
49. King FB. Plants, people and paleoecology. *Illinois State Museum Scientific Papers*, 1984, 20:217.
50. *Amirdowlat Amasyaci. Nenuzhnoe dlja neuczej* [*Needless for ignoramus*]. Nautchnoe nasledstvo. Moscow, Nauka, 1990.

51. Blumenthal M, Goldberg A, Brinkmann J. *Herbal medicine. Expanded Commission E monographs*. Austin, TX, American Botanical Council, 2000:210.
52. Do Monte FH et al. Antinociceptive and anti-inflammatory properties of the hydroalcoholic extract of stems from *Equisetum arvense* L. in mice. *Pharmacological Research*, 2004, 49:239–243.
53. Dos Santos JG et al. Sedative and anticonvulsant effects of hydroalcoholic extracts of *Equisetum arvense*. *Fitoterapia*, 2005, 76:508–513.
54. Grases F et al. Urolithiasis and phytotherapy. *International Journal of Urology and Nephrology*, 1994, 26:507–511.
55. Dornberger K, Lich H. Screening for antimicrobial and presumed cancerostatic plant metabolites. *Pharmazie*, 1982, 37:215–221.
56. Woo WS, Lee EB, Han BH. Biological evaluation of Korean medicinal plants. III. *Archives of Pharmacology*, 1979, 2:127–131.
57. Newton SM et al. The evaluation of forty-three plant species for in vitro antimycobacterial activities; isolation of active constituents from *Psoralea corylifolia* and *Sanguinaria canadensis*. *Journal of Ethnopharmacology*, 2002, 79:57–67.
58. Radulovic N, Stojanovic G, Palic R. Composition and antimicrobial activity of *Equisetum arvense* L. essential oil. *Phytotherapy Research*, 2006, 20:85–88.
59. Turova AD, Sapozhnikova EN. *Lekarstvenn'je rastenija SSSR I ikh primenenije.* Moscow, Meditsina, 1982.
60. Leifertova I, Lisa M. The antifungal properties of higher plants affecting some species of the genus Aspergillus. *Folia Pharm* (Prague), 1979, 2:29–54.
61. Guerin C, Reveillere HP. Antifungal activity of plant extracts used in therapy. I. Study of 41 plant extracts against 9 fungi species. *Annals of Pharmacology*, 1984, 42:553–559.
62. Mlinaric A et al. Screening of selected plant extracts for in vitro inhibitory activity on HIV-1 reverse transcriptase (HIV-1 RT). *Pharmazie*, 2000, 55:75–77.
63. Mekhfi H et al. Platelet anti-aggregant property of some Moroccan medicinal plants. *Journal of Ethnopharmacology*, 2004, 94:317–322.
64. Mineo S et al. Studies on bathing agent I. Anti-inflammatory effect of bathing agent used for skin disease. *Shoyakugaku Zasshi*, 1993, 47:1–4.
65. Myagmar BE, Aniya Y. Free radical scavenging action of medicinal herbs from Mongolia. *Phytomedicine*, 2000, 7:221–222.
66. Nagai T, Myda T, Nagashima T. Antioxidative activities of water extract and ethanol extract from field horsetail (tsukushi) *Equisetum arvense* L. *Food Chemistry*, 2005, 91:389–394.
67. Lee EB. The screening of biologically active plants in Korea using isolated organ preparations. IV. Anticholinergic and oxytocic actions in rat's ileum and uterus. *Korean Journal of Pharmacognosy*, 1982, 13:99–101.
68. Nam SH, Yang MS. Isolation of cytotoxic substances from *Chrysanthemum boreale* M. *Han'guk Nonghwa Hakhoe Chi*, 1995, 38:273–277.

69. Arisawa M. Cell growth inhibition of KB cells by plant extracts. *Natural Medicine*, 1994, 48:338–347.
70. May G, Willuhn G. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. *Arzneimittel-Forschung*, 1978, 28:1–7.
71. Henderson JA, Evans EV, McIntosh RA. The antithiamine action of equisetum. *Journal of American Veterinary Medicine Association*, 1952, 120:375–378.
72. Maeda H, Miyamoto K, Sano T. Occurrence of dermatitis in rats fed a cholesterol diet containing field horsetail (*Equisetum arvense* L.). *Journal of Nutritional Science and Vitaminology*, 1997, 43:553–563.
73. Ladynina EA, Morozova RS. *Fitoterapija*. Leningrad, Meditsina, 1987.
74. Kortikov VN, Kortikov AV. *Polnyi spravotchnik lekarstvennykh rasteni* [*The complete reference of medicinal plants*]. Rostov-na-Donu, Fenix, 2002.
75. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.
76. *British herbal pharmacopoeia*, *Vol. 1.* Keighley, British Herbal Medicine Association, 1983.

Fructus Foeniculi*

Definition

Fructus Foeniculi consists of the dried ripe fruits of *Foeniculum vulgare* Mill. (Apiaceae) (*1–8*).[1]

Synonyms

Anethum foeniculum Clairv., *A. foeniculum* L., *A. rupestre* Salisb., *Feniculum commune* Bubani, *Foeniculum azoricum* Mill., *F. capillaceum* Gilib., *F. dulce* DC., *F. foeniculum* (L.) H. Karst., *F. officinale* All., *F. panmorium* DC., *F. piperitum* DC., *F. sativum* Bertol, *Ligusticum divaricatum* Hoffmannsegg et Link, *L. foeniculum* Crantz, *Meum foeniculum* (L.) Spreng., *Ozodia foeniculacea* Wight et Arn., *Selinum foeniculum* (L.) E.H.L. Krause (*2, 3, 9, 10*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Aneth doux, arap saçi, besbes, bitter fennel, Bitterfenchel, brotanis, common fennel, dill, édeskömény, erva doce, fãnksal, fannel, Fencel, Fenchel, fenchul, Fennekel, fennel, Fennichl, fennikel, Fennkol, fenouil, fenucchiello, fenucchio, fenykl, finkel, Finkel, finichio, finocchio, finucco, fiolho, florence fennel, foenoli doux, funcho, gemeiner Fenchel, Gemüsefenchel, giant fennel, guvamuri, hierba de anis, hinojo, hui-hsiang, imboziso, insilal, koper wloski, lady's chewing tobacco, large fennel, madesi souf, madhurika, marathoron, maratrum, marui, misi, nafa, panmauri, razianeh, razianaj, sanuf, shamar, shomar, sladkij ukrop, sohoehyang, sopu, spingel, sup, thian khaao phlueak, thian klaep, venkel, sweet fennel, uikyo, uikyou, vegetable fennel, vinkel, wild fennel, xiao hui, xiaohuixiang, yi-ra (*2, 3, 6, 8, 9, 11–14*).

---

* Adopted from the volume 3 of WHO monographs on selected medicinal plants.

[1] The European pharmacopoeia (*7*) recognizes Foeniculum vulgare Mill. ssp. vulgare var. vulgare (Foeniculi amari fructus, Bitter Fennel) and F. vulgare Mill. ssp. vulgare var. dulce (Foeniculum dulcis fructus, Sweet Fennel) as distinct entities for which separate monographs are provided. However, in the biological literature, a clear delineation at the variety level is generally not made. Therefore, this monograph has not made the distinction between the "bitter" and "sweet" varieties.

Geographical distribution

Indigenous to the Mediterranean region. Cultivated in Europe, Asia and temperate regions of Africa and South America (*2, 12, 15*).

Description

Perennial aromatic herb, 1–3 m high with green, glaucous, furrowed, branched stems bearing alternate leaves, 2–5 times pinnate with extremely narrow leaflets. Superior leaves with sheaths longer than the blade. Umbels compound, large, nearly regular, on long peduncles. Flowers yellow, no involucre; calyx with five very slight teeth; petals five, entire, tips involute; stamens five; ovary two-celled; stylopodium large, conical. Fruit an oblong cremocarp, 6–10 mm long, 1–4 mm in diameter, greenish; glabrous mericarp compressed dorsally, semicylindrical, with five prominent, nearly regular ribs. Seeds somewhat concave, with longitudinal furrows (*3, 15, 16*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp, oblong 3.5–10.0 mm long, 1–3 mm wide, externally greyish yellow-green to greyish yellow often with pedicel 2–10 mm long. Mericarps usually free, glabrous, each bearing five prominent slightly crenated ridges (*1–4, 7, 8*).

Organoleptic properties

Odour: characteristic, aromatic; taste: sweet to bitter (*1–4, 8*).

Microscopic characteristics

Outer epidermis of the pericarp consists of thick-walled, rectangular, polygonal, colourless cells, with smooth cuticle, few stomata and no hairs. Mesocarp consists of brownish parenchyma; traversed longitudinally by six large schizogenous vittae, appearing elliptical in section and possessing brown epithelial cells; traversed in the ridges by vascular bundles, each having one inner xylem strand and two lateral phloem strands, and accompanied by strongly lignified fibres; some of the mesocarp cells, especially those about the vascular bundles, possess lignified, reticulate cells. Endocarp composed of one layer of flattened thin-walled cells varying in length, but mostly 4–6 µm thick, arranged parallel to one another in groups of five to seven. Endosperm, formed of somewhat thick-walled polygonal cellulosic parenchyma containing fixed oil, several aleurone grains (up to 6 µm in diameter) enclosing a globoid, and one or more mi-

crorosette crystals of calcium oxalate, about 3 µm in diameter. Carpophore often not split, with thick-walled sclerenchyma in two strands (*2*, *8*).

Powdered plant material

Greyish-brown to greyish-yellow. Yellowish-brown-walled polygonal secretory cells, frequently associated with a layer of thin-walled transversely elongated cells 2–9 µm wide, in a parquet arrangement; reticulate parenchyma of the mesocarp; numerous fibre bundles from the ridges, often accompanied by narrow spiral vessels; very numerous endosperm fragments containing aleurone grains, very small microrosette crystals of calcium oxalate, and fibre bundles from the carpophore (*7*).

General identity tests

Macroscopic and microscopic examinations (*1–4*, *7*, *8*), thin-layer chromatography for the presence of anethole and fenchone (*7*), and gas chromatography for the presence of anethole, fenchone and estragole (*7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*17*).

Foreign organic matter

Not more than 1.5% peduncles and not more than 1.5% other foreign matter (*4*, *7*).

Total ash

Not more than 10% (*1*, *4*, *7*, *8*, *18*).

Acid-insoluble ash

Not more than 1.5% (*1*, *2*, *4*).

Water-soluble extractive

Not less than 20% (*3*).

Alcohol-soluble extractive

Not less than 11% (*3*).

Moisture

Not more than 8% (*7*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*19*). For other pesticides, see the *European pharmacopoeia* (*19*) and the WHO guidelines on quality control methods for medicinal plants (*17*) and pesticide residues (*20*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*17*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*17*) for the analysis of radioactive isotopes.

Other purity tests

Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 1.4% v/w essential oil (*1, 2, 4, 6*).

Major chemical constituents

The major constituent is the essential oil (2–6%), which contains *trans*-anethole (50–82%), (+)-fenchone (6–27%), estragole (methylchavicol) (3–20%), limonene (2–13%), *p*-anisaldehyde (6–27%), α-pinene (1–5%) and α-phellandrene (0.1–19.8%) (*9, 12, 14, 21, 22*). Representative structures are presented below.

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of dyspepsia, bloating and flatulence (*9, 23–25*). As an expectorant for mild inflammation of the upper respiratory tract (*24, 26*). Treatment of pain in scrotal hernia, and dysmenorrhoea (*8*).

Uses described in traditional medicine

Treatment of blepharitis, bronchitis, constipation, conjunctivitis, diabetes, diarrhoea, dyspnoea, fever, gastritis, headache, pain, poor appetite and

respiratory and urinary tract infections (*14*). As an aphrodisiac, anthelminthic, emmenagogue, galactagogue and vermicide (*14, 27, 28*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 500 mg/kg body weight (bw) of a 95% ethanol extract of Fructus Foeniculi to mice reduced the perception of pain as measured in the hot-plate test, and decreased yeast-induced pyrexia (*29*). Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats had significant ($P < 0.05$) analgesic activity in the hot-plate reaction test (*30*). In mice with yeast-induced pyrexia, treatment with 500.0 mg/kg bw of the same extract reduced rectal temperature from 36.5 °C to 34.7 °C 90 minutes after administration (*30*).

Antimicrobial activity

An essential oil from the fruits inhibited the growth of *Alternaria* species, *Aspergillus flavus, A. nidulans, A. niger, Cladosporium herbarum, Cunninghamella echinulata, Helminthosporium saccharii, Microsporum gypseum, Mucor mucedo, Penicillium digitatum, Rhizopus nigricans, Trichophyton roseum* and *T. rubrum* in vitro (*31, 32*). In another study, an essential oil was not active against *Aspergillus* species in vitro but a methanol extract of the fruits inhibited the growth of *Helicobacter pylori* (the bacterium associated with gastritis and peptic ulcer disease) in vitro, minimum inhibitory concentration 50.0 µg/ml (*33*). An essential oil from the fruits inhibited the growth of *Candida albicans, Escherichia coli, Lentinus lepideus, Lenzites trabea, Polyporus versicolor, Pseudomonas aeruginosa* and *Staphylococcus aureus* (*34*), and *Kloeckera apiculata, Rhodotorula rubra* and *Torulopsis glabrata* (*35*) in vitro. An ethyl acetate extract of the seeds inhibited the growth of *Shigella flexneri* (*36*), and an 80% ethanol extract of the seeds inhibited the growth of *Bacillus subtilis* and *Salmonella typhi* at concentrations of 250.0 µg/ml in vitro (*37*).

Antispasmodic activity

An ethanol extract of the fruits, 2.5–10.0 ml/l, 1 part fruits:3.5 parts 31% ethanol, inhibited acetylcholine- and histamine-induced guinea-pig ileal contractions in vitro (*23*). An essential oil from the fruits reduced intestinal spasms in mouse intestine, and was 26% as active as papaverine (*38*). Intragastric administration of 2.0–3.0 g/kg bw of an infusion of the fruits to cats inhibited acetylcholine- and histamine-induced ileum spasms by 50% (*39*).

An essential oil from the fruits, 25.0 µg/ml and 10.0 µg/ml, respectively, inhibited oxytocin- and prostaglandin E_2-induced contractions of isolated rat uterus and reduced the frequency of the latter but not the former (*40*).

Cardiovascular effects

Intravenous administration of a 50% ethanol extract of the fruits (dose not specified) reduced blood pressure in dogs (*41*). An aqueous extract of the fruits, 10% in the diet, reduced blood pressure in rats. The effect was abolished by pretreatment of the animals with atropine (*42*). An unspecified extract of the seeds had diuretic effects in rabbits after intragastric administration. The effect was blocked by pretreatment of the animals with morphine (*43*).

Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats induced diuresis. The effect was comparable to that observed in animals treated with 960.0 mg/kg bw of urea, and was almost double that in controls (*30*).

Estrogenic and antiandrogenic activities

Intragastric administration of 2.5 mg/kg bw of an acetone extract of the seeds daily for 15 days to male rats decreased the protein concentration in the testes and vas deferens, and increased it in the seminal vesicles and prostate gland (*44*). The same dose of the same extract administered to female rats daily for 10 days increased the weight of the mammary glands, while higher doses induced vaginal cornification, increased the weight of the oviduct, endometrium, myometrium, cervix and vagina, and induced estrus (*44*). A follow-up study demonstrated that the acetone extract induced cellular growth and proliferation of the endometrium, and stimulated metabolic changes in the myometrium of rats. These changes appeared to favour the survival of spermatocytes and the implantation of the zygote in the uterus (*45*). Conversely, intragastric administration of 2.0 g/kg bw of an aqueous extract of the seeds per day for 25 days significantly ($P < 0.025$) reduced female fertility in mice compared with controls. No effect was observed in male mice (*46*).

Intragastric administration of 0.5 mg/kg bw or 2.5 mg/kg bw of an acetone extract of the fruits per day for 10 days to ovariectomized female rats had estrogenic effects (*45*). Intragastric administration (dose not specified) of an essential oil from the fruits to goats increased the amount of milk produced and the fat content of the milk (*47*). Lactating mice fed the fruits in the diet (concentration not specified) produced pups that ate a larger quantity of fennel-containing foods, suggesting that the constituents of the fruits may be passed in breast milk (*48*). Intragastric administration of

250.0 mg/kg bw of unspecified extracts of the fruits induced estrus and increased the size of the mammary glands and oviducts in adult ovariectomized rats, and exerted an antiandrogenic effect in adult male mice. It also increased the weight of the cervix and vagina of ovariectomized rats, and increased the concentration of nucleic acids and protein in cervical and vaginal tissues. The hyperplasia and hypertrophy of the cervix and vagina were similar to changes seen during estrus in normal female rats (*45*).

Subcutaneous administration of anethole (dose not specified) to sexually immature female rats increased uterine weight and induced estrus. However, in ovariectomized mice the same treatment was not estrogenic (*49*). Intramuscular injection of 100.0 mg/kg bw or 500.0 mg/kg bw of anethole per day for 7 days to rats induced a significant decrease in dorso-lateral prostate weight ($P < 0.05$) (*50*). Intragastric administration of 50.0 mg/kg bw, 70.0 mg/kg bw or 80.0 mg/kg bw of *trans*-anethole to rats had anti-implantation effects, with the maximum effect (100%) at the highest dose (*51*). The compound showed estrogenic effects, and did not demonstrate anti-estrogenic, progestational or androgenic effects (*51*).

Expectorant and secretolytic effects

Application of an infusion of Fructus Foeniculi, 9.14 mg/ml, to isolated ciliated frog oesophagus epithelium increased the transport velocity of fluid by 12%, suggesting an expectorant effect (*52*). Administration of 1.0–9.0 mg/kg bw anethole and 1.0–27.0 mg/kg bw fenchone by inhalation to urethanized rabbits produced a decrease in the specific gravity of the respiratory fluid and enhanced the volume output of respiratory tract fluid (*53*).

Gastrointestinal effects

Intragastric administration of 24.0 mg/kg bw of the fruits increased spontaneous gastric motility in unanaesthetized rabbits; at a dose of 25.0 mg/kg bw the fruits reversed the reduction of gastric motility induced by pentobarbital (*54*).

Sedative effects

Intragastric administration of an essential oil from the fruits (dose not specified) to mice reduced locomotor activity and induced sedation (*55*). A single intraperitoneal administration of 200.0 mg/kg bw of an ether extract of the seeds enhanced barbiturate induced sleeping time in mice. However, intragastric administration of 200.0 mg/kg bw of the extract per day for 7 days decreased barbiturate-induced sleeping time (*56*).

Toxicology

Intragastric administration of 3.0 g/kg bw of a 95% ethanol extract of the fruits induced piloerection and reduced locomotor activity in mice (*30*). Acute (24-hour) and chronic (90-day) oral toxicity studies with an ethanol extract of the fruits were performed in rodents. Acute doses were 0.5 g/kg, 1.0 g/kg and 3.0 g/kg per day; the chronic dose was 100.0 mg/kg per day. No acute or chronic toxic effects were observed (*57*). The acute median lethal dose (LD_{50}) of anethole in rats was 3.8 mg/kg bw after intragastric administration (*58, 59*). Intragastric or subcutaneous administration of 10.0–16.0 g/kg bw of a 50% ethanol extract of the fruits to mice had no toxic effects (*60*). The oral LD_{50} of an essential oil from the fruits in mice was 1326.0 mg/kg bw (*61*).

Chronic use of high doses of *trans*-anethole in rodent dietary studies has been shown to induce cytotoxicity, cell necrosis and cell proliferation. In rats, hepatotoxicity was observed when dietary intake exceeded 30.0 mg/kg bw per day (*62*). In female rats, chronic hepatotoxicity and a low incidence of liver tumours were reported with a dietary intake of trans-anethole of 550.0 mg/kg bw per day, a dose about 100 times higher than the normal human intake (*62*). In chronic feeding studies, administration of *trans*-anethole, 0.25%, 0.5% or 1% in the diet, for 117–121 weeks had no effect on mortality or haematology, but produced a slight increase in hepatic lesions in the treated groups compared with controls (*63*).

Unscheduled DNA synthesis was not induced in vitro by anethole, but was induced by estragole, an effect that was positively correlated with rodent hepatocarcinogenicity (*64*). However, the dose of estragole used (dose not specified) in the rodent studies was much higher than the dose normally administered to humans. Low doses of estragole are primarily metabolized by *O*-demethylation, whereas higher doses are metabolized primarily by 1'-hydroxylation, and the synthesis of 1'-hydroxyestragole, a carcinogenic metabolite of estragole (*65, 66*).

Clinical pharmacology

No information available.

Adverse reactions

In rare cases, allergic reactions such as asthma, contact dermatitis and rhinoconjunctivitis have been reported in sensitive patients (*67, 68*).

Contraindications

The fruits are contraindicated in cases of known sensitivity to plants in the Apiaceae (*69, 70*). Owing to the potential estrogenic effects of the es-

sential oil from the seeds and anethole (*44, 45, 50*), its traditional use as an emmenagogue, and the lack of human studies demonstrating efficacy, Fructus Foeniculi should not be used in pregnancy. Pure essential oils should not be given to infants and young children owing to the danger of laryngeal spasm, dyspnoea and central nervous system excitation (*12*).

Warnings

The pure essential oil from the fruits may cause inflammation, and has an irritant action on the gastrointestinal tract.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the fruits, up to 100.0 mg/ml, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation with homogenized rat liver microsomes (*71, 72*). Aqueous and methanol extracts of the fruits, up to 100.0 mg/ml, were not mutagenic in the *Bacillus subtilis* recombination assay (*71*). However, a 95% ethanol extract, 10.0 mg/plate, was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102 (*73*). An essential oil from the fruits, 2.5 mg/plate, had mutagenic effects in the *Salmonella*/microsome assay in *Salmonella typhimurium* strain TA100 with metabolic activation (*74*), and in the *Bacillus subtilis* recombination assay (*75*). A similar essential oil had no effects in the chromosomal aberration test using Chinese hamster fibroblast cell lines (*76*).

Pregnancy: teratogenic effects

An essential oil from the fruits, up to 500.0 µg/ml, had no teratogenic effects in cultured rat limb bud cells (*61*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds.

Paediatric use

No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds. See also Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test reactions.

Dosage forms

Dried fruits, syrup and tinctures. Store the dried fruits in a well-closed container, protected from light and moisture (*7*).

Posology

(Unless otherwise indicated)

Daily dose: fruits 5–7 g as an infusion or similar preparations, higher daily doses (> 7 g fruits) should not be taken for more than several weeks without medical advice (*25*); fennel syrup or honey 10–20 g; compound fennel tincture 5–7.5 g (5–7.5 ml).

References

1. *Asian crude drugs, their preparations and specifications. Asian pharmacopoeia*. Manila, Federation of Asian Pharmaceutical Associations, 1978.
2. *African pharmacopoeia. Vol. 1*. Lagos, Nigeria, Organization of African Unity, Scientific, Technical and Research Commission, 1985.
3. *Standard of ASEAN herbal medicine. Vol. 1*. Jakarta, ASEAN Countries, 1993.
4. *The Japanese pharmacopoeia*, 13th ed. (English version). Tokyo, Ministry of Health and Welfare, Japan, 1996.
5. *Pharmacopoeia of the Republic of Korea*, 7th ed. Seoul, Taechan yakjon, 1998.
6. *The Ayurvedic pharmacopoeia of India. Part I. Vol. I.* New Delhi, Ministry of Health and Family Welfare, Department of Indian System of Medicine and Homeopathy, 1999.
7. *European pharmacopoeia*, 3rd ed. Suppl. 2001. Strasbourg, Council of Europe, 2000.
8. *Pharmacopoeia of the People's Republic of China. Vol. I* (English ed.). Beijing, China, Chemical Industry Press, 2000.
9. Hänsel R et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Bd 5, Drogen E–O*, 5th ed. [Hager's handbook of pharmaceutical practice. Vol. 5, Drugs E–O, 5th ed.] Berlin, Springer, 1993.
10. Tanaka T. ed. *Nippon Yakuso Zensho.* [Encyclopedia of Japanese Medicinal Plants.] Tokyo, Shin-Nihon Shuppan, 1995 [in Japanese].
11. Bensky D, Gamble A, Kaptchuk T, eds. *Chinese herbal medicine, materia medica*, rev. ed. Seattle, WA, Eastland Press, 1993.
12. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
13. Holmes P. *The energetics of western herbs. Vol. 1*, rev. 3rd ed. Boulder, CO, Snow Lotus, 1997.

14. Farnsworth NR, ed. *NAPRALERT database.* Chicago, IL, University of Illinois at Chicago, 9 February 2001 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
15. *Medicinal plants in China*. Manila, World Health Organization Regional Office for the Western Pacific, 1989 (WHO Regional Publications, Western Pacific Series, No. 2).
16. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, PA, Blakiston, 1950.
17. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
18. *British herbal pharmacopoeia*. Exeter, British Herbal Medicine Association, 1996.
19. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
20. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (WHO/FSF/FOS/97.7; available from Food Safety, World Health Organization, 1211 Geneva 27, Switzerland).
21. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier Publishing, 1995.
22. *The Japanese pharmacopoeia 13th edition commentary*. Tokyo, Hirokawa Shoten, 1996 [in Japanese].
23. Forster HB, Niklas H, Lutz S. Antispasmodic effects of some medicinal plants. *Planta Medica*, 1980, 40:309–319.
24. Weiss RF. *Lehrbuch der Phytotherapie*, 7th ed. [Textbook of phytotherapy, 7th ed.] Stuttgart, Hippokrates, 1991.
25. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
26. Reynolds JEF, ed. Fennel, fennel oil. In: *Martindale – the extra pharmacopoeia*, 30th ed. London, The Pharmaceutical Press, 1993.
27. Hare HA, Caspari C, Rusby HH. *The national standard dispensatory.* Philadelphia, PA, Lea and Febiger, 1916.
28. Albert-Puleo M. Fennel and anise as estrogenic agents. *Journal of Ethnopharmacology*, 1980, 2:337–344.
29. Mascolo N et al. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytotherapy Research*, 1987 1:28–31.
30. Tanira MOM et al. Pharmacological and toxicological investigations on *Foeniculum vulgare* dried fruit extract in experimental animals. *Phytotherapy Research*, 1996, 10:33–36.
31. Sharma SK, Singh VP. The antifungal activity of some essential oils. *Indian Drugs and Pharmaceuticals Industry*, 1979, 14:3–6.
32. Dikshit A, Husain A. Antifungal action of some essential oils against animal pathogens. *Fitoterapia*, 1984, 55:171–176.

33. Mahady GB et al. In vitro susceptibility of *Helicobacter pylori* to botanicals used traditionally for the treatment of gastrointestinal disorders. *Phytomedicine*, 2000, 7(Suppl. II): 95.
34. Janssen AM et al. Screening for antimicrobial activity of some essential oils by the agar overlay technique. *Pharmazeutisch Weekblad (Scientific Edition)*, 1986, 8:289–292.
35. Conner DE, Beuchat LR. Effects of essential oils from plants on growth of food spoilage yeast. *Journal of Food Science*, 1984, 49:429–434.
36. Jimenez Misas CA, Rojas Hernandez NM, Lopez Abraham AM. Contribución a la evaluación biológica de plantas cubanas. III. [The biological assessment of Cuban plants. III.] *Revista Cubana de Medicina Tropicale*, 1979, 31:21–27.
37. Izzo AA et al. Biological screening of Italian medicinal plants for antibacterial activity. *Phytotherapy Research*, 1995, 9:281–286.
38. Haginiwa J, Harada M, Morishita I. [Pharmacological studies on crude drugs VII. Properties of essential oil components of aromatics and their pharmacological effects on mouse intestine.] *Yakugaku Zasshi*, 1963, 83:624–628 [in Japanese].
39. Schuster KP. Wirkungstärke und Wirkungsverluste spasmolytische wirksamer Arzneidrogen, galenischer Zubereitungen und Arzneifertigwaren, geprüft am isolierten Darm des Meerschweinchens und am Darm der Katze in situ. [Intensity and loss of the in situ effect of spasmolytically active drugs, galenic preparations (crude drugs) and galenic drugs in finished dosage form, on isolated gut of guinea-pig and cat.] Dissertation, University of Munich, 1971.
40. Ostad SN et al. The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study. *Journal of Ethnopharmacology*, 2001, 76:299–304.
41. Mokkhasmit M et al. Pharmacological evaluation of Thai medicinal plants. *Journal of the Medical Association of Thailand*, 1971, 54:490–504.
42. Haranath PSRK, Akther MH, Sharif SI. Acetylcholine and choline in common spices. *Phytotherapy Research*, 1987, 1:91–92.
43. Skovronskii VA. [The effect of caraway, anise, and of sweet fennel on urine elimination.] *Sbornik nauchnikh trudov l'vovskogo veterinarno-zootekhnicheskogo instituta*, 1953, 6:275–282 [in Russian].
44. Malini T et al. Effect of *Foeniculum vulgare* Mill seed extract on the genital organs of male and female rats. *Indian Journal of Physiology and Pharmacology*, 1985, 29:21–26.
45. Annusuya S et al. Effect of *Foeniculum vulgare* seed extracts on cervix and vagina of ovariectomised rats. *Indian Journal of Medical Research*, 1988, 87:364–367.
46. Alkofahi A, Al-Hamood MH, Elbetieha AM. *Archives of Sexually Transmitted Diseases and Human Immunodeficiency Virus Research*, 1996, 10:189–196.

47. Mills S, Bone K. *Principles and practice of phytotherapy*. Edinburgh, Churchill Livingstone, 2000.
48. Shukla HS, Upadhyay PD, Tripathi SC. Insect repellent properties of essential oils of *Foeniculum vulgare*, *Pimpinella anisum* and anethole. *Pesticides*, 1989, 23:33–35.
49. Zondek B, Bergmann E. Phenol methyl esters as oestrogenic agents. *Biochemical Journal*, 1938, 32:641–643.
50. Farook T et al. Effect of anethole on accessory sex tissue of albino rats. *Journal of Research in Ayurvedic Science*, 1989, 15:167–170.
51. Dhar SK. Anti-fertility activity and hormonal profile of *trans*-anethole in rats. *Indian Journal of Physiology and Pharmacology*, 1995, 39:63–67.
52. Müller-Limmroth W, Fröhlich HH. Wirkungsnachweis einiger phytotherapeutischer Expektorantien auf den mukoziliaren Transport. [Effect of various phytotherapeutic expectorants on mucociliary transport.] *Fortschrift für Medizin*, 1980, 98:95–101.
53. Boyd EM, Sheppard EP. An autumn-enhanced mucotropic action of inhaled terpenes and related volatile agents. *Pharmacology*, 1971, 6:65–80.
54. Niiho Y, Takayanagi I, Takagi K. Effects of a combined stomachic and its ingredients on rabbit stomach motility in situ. *Japanese Journal of Pharmacology*, 1977, 27:177–179.
55. Shipochliev T. [Pharmacological research into a group of essential oils. II. Effect on the motor activity and general state of white mice in separate applications or after iproniazid phosphate.] *Veterinarno-Meditsinski Nauki*, 1968, 5:87–92 [in Bulgarian].
56. Han YB, Shin KH, Woo WS. Effect of spices on hepatic microsomal enzyme function in mice. *Archives of Pharmacal Research*, 1984, 7:53–56.
57. Shah AH, Qureshi S, Ageel AM. Toxicity studies in mice of ethanol extracts of *Foeniculum vulgare* fruit and *Ruta chalepensis* aerial parts. *Journal of Ethno-pharmacology*, 1991, 34:167–172.
58. Opdyke DLJ. Monographs on fragrance raw materials: fennel oil. *Food and Cosmetics Toxicology*, 1974, 12:879–880.
59. Opdyke DLJ. Monographs on fragrance raw materials: fennel oil, bitter. *Food and Cosmetics Toxicology*, 1976, 14:309.
60. Mokkhasmit M et al. Study on the toxicity of Thai medicinal plants. *Bulletin of the Department of Medical Science*, 1971, 12:36–65.
61. Ostad SN, Khakinegad B, Sabzevari O. The study of teratogenic effect of fennel essential oil in vitro. *Toxicology Letters*, 2000, 116:89 [abstract].
62. Newberne P et al. The FEMA GRAS assessment of *trans*-anethole used as a flavouring substance. *Food and Chemical Toxicology*, 1999, 37:789–811.
63. Truhaut R et al. Chronic toxicity/carcinogenicity study of *trans*-anethole in rats. *Food and Chemical Toxicology*, 1989, 27:11–20.
64. Howes AJ, Chan VS, Caldwell J. Structure-specificity of the genotoxicity of some naturally occurring alkenylbenzenes determined by the unscheduled

DNA synthesis assay in rat hepatocytes. *Food and Chemical Toxicology*, 1990, 28:537–542.

65. Fennel TR et al. Major role of hepatic sulfotransferase activity in the metabolic activation, DNA adduct formation, and carcinogenicity of 1'-hydroxy-2',3'-dehydroestragole in infant male C57BL/J66 × C3H/HeJ F1 mice. *Cancer Research*, 1985, 45:5310–5320.
66. Anthony A et al. Metabolism of estragole in rat and mouse and influence of dose size on excretion of the proximate carcinogen 1'-hydroxyestragole. *Food and Chemical Toxicology*, 1987, 25:799–806.
67. Jensen-Jarolim E et al. Characterization of allergens in Apiaceae spices: anise, fennel, coriander and cumin. *Clinical and Experimental Allergy*, 1997, 27:1299–1306.
68. Schwartz HJ et al. Occupational allergic rhinoconjunctivitis and asthma due to fennel seed. *Annals of Allergy, Asthma and Immunology*, 1997, 78:37–40.
69. Wüthrich B, Hoffer T. Nahrungsmittelallergie: das Sellerie-Beifuss-Gerwürz-Syndrom. Assoziation mit einer Mangofrucht-Allergie? [Food allergy: the celery-mugwort-spice syndrome. Association with mango allergy?] *Deutsche medizinische Wochenschrift*, 1984, 109:981–986.
70. Stäger J, Wuthrich B, Johansson SG. Spice allergy in celery-sensitive patients. *Allergy*, 1991, 46:475–478.
71. Morimoto I et al. Mutagenicity screening of crude drugs with *Bacillus subtilis rec*-assay and *Salmonella*/microsome reversion assay. *Mutation Research*, 1982, 97:81–102.
72. Yamamoto H, Mizutani T, Nomura H. [Studies on the mutagenicity of crude drug extracts. I.] *Yakugaku Zasshi*, 1982, 102:596–601 [in Japanese].
73. Mahmoud I et al. Mutagenic and toxic activities of several spices and some Jordanian medicinal plants. *International Journal of Pharmacognosy*, 1991, 30:81–85.
74. Marcus C, Lichtenstein EP. Interactions of naturally occurring food plant components with insecticides and pentobarbital in rats and mice. *Journal of Agricultural and Food Chemistry*, 1982, 30:563–568.
75. Sekizawa J, Shibamoto T. Genotoxicity of safrole-related chemicals in microbial test systems. *Mutation Research*, 1982, 101:127–140.
76. Ishidate M et al. Primary mutagenicity screening of food additives currently used in Japan. *Food and Chemical Toxicology*, 1984, 22:623–636.

Radix Ginseng*

Definition

Radix Ginseng is the dried root of *Panax ginseng* C.A. Meyer (Araliaceae) (*1–5*).[1]

Synonyms

Panax schinseng Nees (*2*).

Other *Panax* species, including *P. quinquefolius* L. (American ginseng), *P. notoginseng* Burk. (San-chi ginseng), *P. pseudoginseng* Wall. ssp. *japonicus* Hara = *P. japonicus* C.A. Meyer (Japanese chikutsu ginseng) and *P. notoginseng* ssp. *himalaicus* (Himalayan ginseng) have also been referred to as "ginseng" and used medically (*6*, *7*). However, scientific documentation of these species is insufficient to justify the preparation of a monograph at this time.

Selected vernacular names

Chosen ninjin, ginseng, Ginsengwurzel, hakusan, hakushan, higeninjin, hongshen, hungseng, hungshen, hunseng, jenseng, jenshen, jinpi, kao-liseng, Korean ginseng, minjin, nhan sam, ninjin, ninzin, niuhuan, Oriental ginseng, otane ninjin, renshen, san-pi, shanshen, sheng-sai-seng, shenshaishanshen, shengshaishen, t'ang-seng, tyosenninzin, yakuyo ninjin, yakuyo ninzin, yeh-shan-seng, yuan-seng, yuanshen (*1*, *2*, *4–10*).

Description

A perennial herb with characteristic branched roots extending from the middle of the main root in the form of a human figure. Stem erect, simple, and not branching. Leaves verticillate, compound, digitate, leaflets 5, with the 3 terminal leaflets larger than the lateral ones, elliptical or slightly

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.

[1] Steamed Panax ginseng root is listed in the Japanese pharmacopoeia as "Red Ginseng (Ginseng Radix Rubra)" (2).

obovate, 4–15 cm long by 2–6.5 cm wide; apex acuminate; base cuneate; margin serrulate or finely bidentate. In general, 1 leaf in the first year with 1 leaflet added annually until the sixth year. Inflorescence a small terminal umbel, hemispherical in early summer. Flowers polygamous, pink. Calyx vaguely 5-toothed. Petals 5, stamens 5. Fruit a small berry, nearly drupaceous, and red when ripe in autumn (*8*).

Plant material of interest: dried root

General appearance

The main root is fusiform or cylindrical, 2.5–20 cm long by 0.5–3.0 cm in diameter; externally greyish yellow; upper part or entire root exhibiting sparse, shallow, interrupted, and coarse transverse striations and distinct longitudinal wrinkles; lower part bearing 2–5 branching lateral roots and numerous slender rootlets with inconspicuous minute tubercles. Rhizomes 1–4 cm long by 0.3–1.5 cm in diameter, mostly constricted and curved, bearing adventitious roots and sparse depressed circular stem scars. Texture relatively hard, fracture yellowish white, cambium ring brownish yellow, starchy (*1–5*).

Organoleptic properties

Colour, greyish white to amber-yellow; odour, characteristic; taste, slightly sweet at first, followed by a slight bitterness (*1*, *2*).

Microscopic characteristics

The transverse section shows cork consisting of several rows of cells; cortex narrow; phloem showing clefts in the outer part, and parenchymatous cells densely arranged and scattered with resin canals containing yellow secretions in the inner part; cambium in a ring; xylem rays broad, vessels singly scattered or grouped in an interrupted radial arrangement, and occasionally accompanied by non-lignified fibres; parenchyma cells containing abundant starch grains and a few clusters of calcium oxalate (*1*, *3–5*).

Powdered plant material

Yellowish white; fragments of resin canals containing yellow secretions; clusters of calcium oxalate (20–68 µm in diameter), few, with acute angles; cork cells subsquare or polygonal, with thin and sinuous walls; reticulate and scalariform vessels 10–56 µm in diameter; starch granules fairly abundant, simple, subspheroidal, semicircular, or irregular polygonal (4–30 µm in diameter), singly or in groups of two to four (*1–5*).

Geographical distribution

Mountain regions of China (Manchuria), the Democratic People's Republic of Korea, Japan, the Republic of Korea, and the Russian Federation (eastern Siberia) (*7*, *8*). It is commercially produced mainly by cultivation (*6*).

General identity tests

Macroscopic and microscopic examinations, microchemical tests, and thin-layer chromatographic analysis (*1–5*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Ginseng products should be negative. The maximum acceptable limits of other microorganisms are as follows (*11–13*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Foreign organic matter

Not more than 2% (*2*, *3*).

Total ash

Not more than 4.2% (*2*).

Acid-insoluble ash

Not more than 1% (*4*).

Sulfated ash

Not more than 12% (*5*).

Alcohol-soluble extractive

Not less than 14.0% (*2*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Ginseng is not more than 0.05 mg/kg (*13*). For other pesticides, see WHO guidelines on

quality control methods for medicinal plants (*11*) and guidelines for predicting dietary intake of pesticide residues (*14*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*11*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*11*).

Other purity tests

Chemical and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

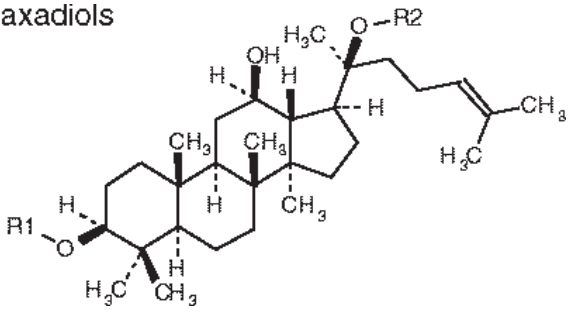
Microchemical, thin-layer chromatographic, and spectrophotometric methods are used for the qualitative and quantitative analysis of ginsenosides (*1–5*). High-performance liquid chromatography (*15–17*) and liquid chromatography–mass spectrometry (*18*) methods are also available.

Characteristic saponins known as ginsenosides, not less than 1.5% calculated as ginsenoside Rg_1 (D-glucopyranosyl-6β-glucopyranosyl-20*S*-protopanaxatriol, relative molecular mass 800) (*3*, *5*).

Major chemical constituents

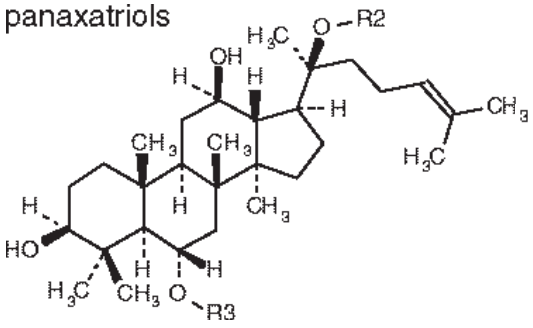
The major chemical constituents are triterpene saponins. More than 30 are based on the dammarane structure, and one (ginsenoside Ro) is derived from oleanolic acid (*6*, *7*, *17*, *19*). The dammarane saponins are derivatives of either protopanaxadiol or protopanaxatriol. Members of the former group include ginsenosides Ra_{1-3}, Rb_{1-3}, Rc, Rc_2, Rd, Rd_2, and Rh_2; (20*S*)-ginsenoside Rg_3; and malonyl ginsenosides Rb_1, Rb_2, Rc, and Rd. Examples of protopanaxatriol saponins are ginsenosides Re_2, Re_3, Rf, Rg_1, Rg_2, and Rh_1; 20-gluco-ginsenoside Rf; and (20*R*)-ginsenosides Rg_2 and Rh_1. Those considered most important are ginsenosides Rb_1, Rb_2, Rc, Rd, Rf, Rg_1, and Rg_2; Rb_1, Rb_2, and Rg_1 are the most abundant. Representative structures are presented below.

panaxadiols

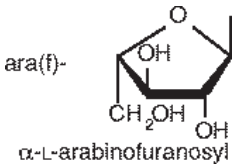


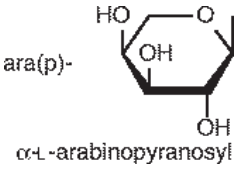
	R1	R2
ginsenoside Rb_1	*O*-glc-(1→2)-glc-	*O*-glc-(1→6)-glc-
ginsenoside Rb_2	*O*-glc-(1→2)-glc-	*O*-ara(p)-(1→6)-glc-
ginsenoside Rc	*O*-glc-(1→2)-glc-	*O*-ara(f)-(1→6)-glc-
ginsenoside Rd	*O*-glc-(1→2)-glc-	glc-

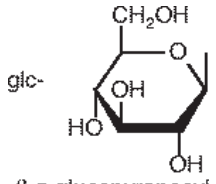
panaxatriols

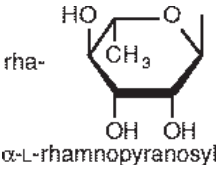


	R2	R3
ginsenoside Re	glc-	*O*-rha-(1→2)-glc-
ginsenoside Rf	H-	*O*-glc-(1→2)-glc-
ginsenoside Rg_1	glc-	glc-
ginsenoside Rg_2	H-	*O*-rha-(1→2)-glc-









Dosage forms

Crude plant material, capsules and tablets of powdered drugs, extracts, tonic drinks, wines, and lozenges. Store in a cool, dry place in well-sealed containers (*20*).

Medicinal uses

Uses supported by clinical data

Radix Ginseng is used as a prophylactic and restorative agent for enhancement of mental and physical capacities, in cases of weakness, exhaustion, tiredness, and loss of concentration, and during convalescence (*21–29*).

Uses described in pharmacopoeias and in traditional systems of medicine

Radix Ginseng has been used clinically in the treatment of diabetes (*1*), but further clinical studies are needed. The drug is also used in the treatment of impotence, prevention of hepatotoxicity, and gastrointestinal disorders such as gastritis and ulcers (*1*, *7*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of liver disease, coughs, fever, tuberculosis, rheumatism, vomiting of pregnancy, hypothermia, dyspnoea, and nervous disorders (*7*).

Pharmacology

Experimental pharmacology

The suggested mode of action of Radix Ginseng is twofold. First, the drug has an "adaptogenic" effect (*30*), which produces a non-specific increase

in the body's own defences against exogenous stress factors and noxious chemicals (*31*). Secondly, the drug promotes an overall improvement in physical and mental performance (*30–33*).

Treatment of cultured mammalian cells, isolated organs, and animal models (primarily mice and rats) with Radix Ginseng before or during exposure to physical, chemical, or psychological stress increased the ability of the respective model systems to resist the damaging effects of various stressors (*31*). These results were demonstrated in cases of radiation poisoning (*34–36*), viral infection and tumour load (*37*, *38*), alcohol or carbon tetrachloride poisoning (*39–41*), oxygen deprivation and hypobaric pressure (*42*, *43*), light or temperature stress, emotional stress, and electrical shock or restricted movement (*44*, *45*, *46*). The mechanism by which the drug exerts its activity is most likely through the hypothalamus–pituitary–adrenal axis (*47–49*) and through its immunostimulant effect (*50*).

Intraperitoneal administration to rats of ginseng saponin fractions or the ginsenosides Rb_1, Rb_2, Rc, Rd, and Re elevated serum levels of adrenocorticotropic hormone (ACTH) and corticosterone (*51*, *52*). Pretreatment with dexamethasone, which blocks hypothalamus and pituitary functions, prevented ginseng saponin-mediated release of ACTH and corticosterone, and thereby demonstrated that the increase in serum corticosterone by ginseng occurs indirectly through release of ACTH from the pituitary (*51*, *52*).

The immunomodulatory activity of ginseng appears to be at least partly responsible for its adaptogenic effect (*50*, *53*, *54*). Alcohol extracts of Radix Ginseng stimulated phagocytosis in vitro, were mitogenic in cultured human lymphocytes, stimulated the production of interferon, and enhanced the activity of natural killer cells (*55*, *56*). Intraperitoneal administration of an extract of the drug to mice stimulated cell-mediated immunity against Semliki Forest virus, elevated antibody levels against sheep red blood cells and natural killer cells (*57*), and stimulated the production of interferon (*58*).

Improvement in physical and mental performance has been observed in mice and rats after oral or intraperitoneal administration of the drug (*59–63*). Oral administration of ginseng saponin fractions to mice increased endurance and prolonged swimming time in swimming tests (*63*). However, two studies concluded that ginseng had no positive effects on the physical performance in mice and rats (*64*, *65*). The adaptogenic effects of Radix Ginseng are generally attributed to the ginsenosides (*66*, *67*). The ginsenosides have been shown to alter mechanisms of fuel homeostasis during prolonged exercise, by increasing the capacity of skeletal muscle to oxidize free fatty acids in preference to glucose for cellular en-

ergy production (*59*). Other constituents of Radix Ginseng, such as vanillic and salicylic acid, have also been reported to have "antifatigue" activity in rats (*68*). Furthermore, the antioxidant activity of ginseng was associated with both the ginsenosides and the flavonoid constituents (*31*, *69*). The ginsenosides protected pulmonary vascular endothelium against free-radical-induced injury (*69*).

Mice given ginseng extract or ginsenosides Rb_1 and Rg_2 orally during passive avoidance response tests showed an improvement in learning ability which was negatively influenced by stress (*30*), and rats showed improved retention of learned behaviour (*70*). Ginsenosides Rg_1 and Rb_1 are the active nootropic constituents of the drug (*66*), and improve memory and learning in normal as well as cognition-impaired animals. The mode of action involves an increase in the synthesis and release of acetylcholine, and a decrease of brain serotonin levels (*66*). In cerebral and coronary blood vessels, extracts of Radix Ginseng produced vasodilatation, which improved brain and coronary blood flow (*71*). The vasodilatory activity of the ginsenosides appears to be primarily due to relaxation of vascular smooth muscles. The ginsenosides block the constricting effects of norepinephrine in isolated aorta strips, and inhibit the uptake of $^{45}Ca^{2+}$ in the membrane and sarcolemma of rabbit heart tissue. Inhibition of Ca^{2+} uptake in the muscle membrane contributes to the mechanism of vasodilatation (*71*).

A number of polypeptides and glycans isolated from Radix Ginseng, named GP and panaxans A–E, respectively, have demonstrated hypoglycaemic activity when given intraperitoneally to mice (*72*, *73*). Two of the glycans, panaxans A and B, have been shown to stimulate hepatic glucose utilization by increasing the activity of glucose-6-phosphate 1-dehydrogenase, phosphorylase *a*, and phosphofructokinase (*72*). Panaxan A did not affect plasma insulin levels or insulin sensitivity, but panaxan B elevated the plasma insulin level by stimulating insulin secretion from pancreatic islets, and further enhanced insulin sensitivity by increasing insulin binding to receptors (*72*). The panaxans are not active after oral administration. Administration of GP (intravenously or subcutaneously) to mice or rats decreased blood glucose and liver glycogen levels (*73*). Radix Ginseng also contains a number of other constituents with hypoglycaemic activity (*72*, *74*). Adenosine, isolated from a water extract of Radix Ginseng, enhanced lipogenesis and cyclic AMP accumulation of adipocytes, and some of the ginsenosides inhibited ACTH-induced lipolysis, suppressed insulin-stimulated lipogenesis, and stimulated the release of insulin from cultured islets (*72*).

Subcutaneous administration of a ginseng extract enhanced the mating behaviour of male rats (*75*). The drug further stimulated spermatogenesis

in rat (*76*), and rabbit testes, and increased the motility and survival of rabbit sperm outside the body (*75*).

Intragastric or intradermal administration of an ethanol extract of the drug to rats decreased histamine-, pentagastrin-, carbachol- and vagal stimulation-induced gastric secretion, and inhibited gastric ulcers induced by stress or by pyloric ligation (*77–79*).

Liver-protectant activity of ginseng has been demonstrated in vitro and in vivo (*80*, *81*). Intraperitoneal administration of Radix Ginseng extracts to normal and dexamethasone-treated rats did not influence the blood chemistry of normal rats, but it decreased aspartate aminotransferase and alanine aminotransferase levels in dexamethasone-treated animals, thereby demonstrating a liver-protectant effect (*81*). However, another study demonstrated that an intraperitoneal injection of a methanol extract of Radix Ginseng had no protective activity against carbon tetrachloride-induced hepatotoxicity in rats (*82*).

Clinical pharmacology

Antifatigue activity

The results of clinical studies measuring increased performance and antifatigue effects of ginseng extracts are conflicting and, in general, most studies suffer from poor methodology, lack of proper controls, and no standardization of the ginseng extracts used. The influence of chronic Radix Ginseng administration (2 g/day orally for 4 weeks) on substrate utilization, hormone production, endurance, metabolism, and perception of effort during consecutive days of exhaustive exercise in 11 naval cadets was reported. No significant differences were observed between the control group and the group receiving the ginseng supplementation (*83*). Another clinical trial with eight participants reported no significant difference between placebo and ginseng administration during exhaustive exercise after 7 days of treatment (*84*). A randomized, double-blind, cross-over study sought the effects of ginseng on circulatory, respiratory, and metabolic functions during maximal exercise in 50 men (21–47 years old) (*24*). Total tolerated workload and maximal oxygen uptake were significantly higher following ginseng administration than with placebo. At the same workload, oxygen consumption, plasma lactate levels, ventilation, carbon dioxide production, and heart rate during exercise were all lower in the ginseng treatment group. The results indicated that the ginseng preparations effectively increased the work capacity of the participants by improving oxygen utilization (*24*). A placebo-controlled, cross-over study determined the effects of ginseng on the physical fitness of 43 male triathletes (*25*). The participants received 200 mg of a ginseng

preparation twice daily for two consecutive training periods of 10 weeks. No significant changes were observed during the first 10-week period, but ginseng appeared to prevent the loss of physical fitness (as measured by oxygen uptake and oxygen pulse) during the second 10-week period (*25*). Two further studies with athletes given 100 mg of a standardized ginseng extract twice daily for 9 weeks reported significant improvement in aerobic capacity and reduction in blood lactate and heart rates (*26*, *27*), but placebos or controls were not used in either of the two studies. Further extension of these studies using placebo-controlled, double-blind trials demonstrated significant improvement in the ginseng group as compared with the placebo group (*28*). Similar results were reported in another study on athletes, and the differences between the ginseng and placebo groups lasted for approximately 3 weeks after the last ginseng dose (*29*). The effects of 1200 mg of Radix Ginseng in a placebo-controlled, double-blind cross-over study in fatigued night nurses were assessed and the results were compared with placebo and with effects on nurses engaged in daytime work (*22*). Ginseng restored ratings on tests of mood, competence, and general performance, and the study concluded that ginseng had anti-fatigue activity (*22*).

Aqueous and standardized ginseng extracts were tested in a placebo-controlled, double-blind study for immunomodulatory actions (*85*). Sixty healthy volunteers were divided into three groups of 20 each and were given either a placebo or 100 mg of aqueous ginseng extract or 100 mg of standardized ginseng extract, every 12 hours for 8 weeks. Blood samples drawn from the volunteers revealed an increase in chemotaxis of polymorphonuclear leukocytes, the phagocytic index, and the total number of T3 and T4 lymphocytes after 4 and 8 weeks of ginseng therapy, as compared with the placebo group. The group receiving the standardized extract also increased their T4:T8 ratio and the activity of natural killer cells. The conclusion of this study was that ginseng extract stimulated the immune system in humans, and that the standardized extract was more effective than the aqueous extract (*85*).

Psychomotor activity

A double-blind, placebo-controlled clinical study assessed the effect of standardized ginseng extract (100 mg twice daily for 12 weeks) on psychomotor performance in 16 healthy individuals (*23*). Various tests of pyschomotor performance found a favourable effect on attention, processing, integrated sensory–motor function, and auditory reaction time. The study concluded that the drug was superior to the placebo in improving certain psychomotor functions in healthy subjects (*23*).

Antidiabetic activity
Radix Ginseng has been shown in clinical studies to have beneficial effects in both insulin-dependent and non-insulin-dependent diabetic patients (*86*, *87*). Oral administration of ginseng tablets (200 mg daily for 8 weeks) to 36 non-insulin-dependent patients elevated mood, improved physical performance, reduced fasting blood glucose and serum aminoterminal propeptide of type III procollagen concentrations, and lowered glycated haemoglobin (*87*).

Impotence
Ginseng extracts improved sperm production in men and may have some usefulness in treating impotence (*32*). The ginsenosides, which appear to be the active components, are thought to depress blood prolactin levels, thereby increasing libido (*32*). In one clinical study, 90 patients with erectile dysfunction were treated with ginseng saponins (600 mg orally per day). Treatment improved rigidity, tumescence, and libido, but not the frequency of coitus (*88*).

Contraindications
None (*21*, *50*, *89*, *90*).

Warnings
No information available.

Precautions

General
Diabetic patients should consult a physician prior to taking Radix Ginseng, as ginseng intake may slightly reduce blood glucose levels (*86*, *87*).

Drug interactions
There are two reports of an interaction between Radix Ginseng and phenelzine, a monoamine oxidase inhibitor (*91*, *92*). The clinical significance of this interaction has not been evaluated.

Drug and laboratory test interactions
None reported.

Carcinogenesis, mutagenesis, impairment of fertility
Radix Ginseng is not carcinogenic or mutagenic in vitro, and does not have any effect on fertility (*90*).

Pregnancy: teratogenic effects
Radix Ginseng is not teratogenic in vivo (*90*).

Pregnancy: non-teratogenic effects
The safety of Radix Ginseng for use in pregnancy has not been established.

Nursing mothers
Excretion of Radix Ginseng compounds into breast milk and its effects on the newborn have not been established.

Paediatric use
The safety and efficacy of Radix Ginseng use in children have not been established.

Adverse reactions
Various researchers who studied Radix Ginseng extracts using conventional toxicological methods in five different animal models reported no acute or chronic toxicity of the extract (*89*, *90*, *93*).

On the basis of Radix Ginseng's long use, and the relative infrequency of significant demonstrable side-effects, it has been concluded that the use of Radix Ginseng is not associated with serious adverse effects if taken at the recommended dose (*90*, *93*). However, in Siegel's open study of 133 patients ingesting large quantities, ginseng was reported to result in hypertension, nervousness, irritability, diarrhoea, skin eruptions, and insomnia, which were collectively called ginseng abuse syndrome (GAS) (*94*). Critical analysis of this report has shown that there were no controls or analyses to determine the type of ginseng being ingested or the constituents of the preparation taken, and that some of the amounts ingested were clearly excessive (as much as 15 g per day, where the recommended daily dose is 0.5–2 g) (*50*, *90*, *95*). When the dose was decreased to 1.7 g/day the symptoms of the "syndrome" were rare. Thus the only conclusion that can be validly extracted from the Siegel study is that the excessive and uncontrolled intake of ginseng products should be avoided (*90*). One case of ginseng-associated cerebral arteritis has been reported in a patient consuming a high dose of an ethanol extract of ginseng root (approximately 6 g in one dose) (*96*). However, again the type and quantity of ginseng extract were not reported. Two cases of mydriasis and disturbance in accommodation, as well as dizziness have been reported after ingestion of large doses (3–9 g) of an unspecified type of ginseng preparation (*97*).

Estrogenic-like side-effects have been reported in both premenopausal and postmenopausal women following the use of ginseng. Seven cases of mastalgia (*98–100*) and one case of vaginal bleeding in a postmenopausal woman (*101*) were reported after ingestion of unspecified ginseng products. An increased libido in premenopausal women has also been reported (*100*). Specific studies on the possible hormonal side-effects of ginseng have been carried out with a standardized ginseng extract (*102–104*). Under physiological conditions, there is no interaction of the ginseng extract with either cytosolic estrogen receptors isolated from mature rat uterus or progesterone receptors from human myometrium (*102*). Furthermore, clinical studies have demonstrated that a standardized ginseng extract does not cause a change in male and female hormonal status (*103*, *104*).

Posology

Unless otherwise prescribed, daily dose (taken in the morning): dried root 0.5–2 g by decoction; doses of other preparations should be calculated accordingly (*21*, *23*, *89*).

References

1. *Pharmacopoeia of the People's Republic of China* (English ed.). Guangzhou, Guangdong Science and Technology Press, 1992.
2. *The pharmacopoeia of Japan XII*. Tokyo, The Society of Japanese Pharmacopoeia, 1991.
3. *Pharmacopée française*. Paris, Adrapharm, 1996.
4. *Deutsches Arzneibuch 1996.* Stuttgart, Deutscher Apotheker Verlag, 1996.
5. *Pharmacopoeia helvetica VII*. Berne, Département fédéral de l'intérieur, 1994.
6. Shibata S et al. Chemistry and pharmacology of *Panax*. In: Wagner H, Farnsworth NR, Hikino H, eds. *Economic and medicinal plants research*, *Vol. 1*. London, Academic Press, 1985.
7. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
8. *Medicinal plants in China*. Manila, World Health Organization, 1989 (WHO Regional Publications, Western Pacific Series, No. 2).
9. Hsu HY. *Oriental materia medica, a concise guide*. Long Beach, CA, Oriental Healing Arts Institute, 1986.
10. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, August 8, 1995 production (an on-line database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).

11. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
12. *Deutsches Arzneibuch 1996. Vol. 2. Methoden der Biologie*. Stuttgart, Deutscher Apotheker Verlag, 1996.
13. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1997.
14. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (unpublished document WHO/FSF/FOS/97.7; available from Food Safety, WHO, 1211 Geneva 27, Switzerland).
15. Sticher O, Soldati F. HPLC separation and quantitative determination of ginsenosides from *Panax ginseng, Panax quinquefolium* and from ginseng drug preparations. 1. *Planta medica*, 1979, 36:30–42.
16. Sticher O, Soldati F. HPLC separation and quantitative determination of ginsenosides from *Panax ginseng*, *Panax quinquefolium* and from ginseng drug preparations. 2. *Planta medica*, 1979, 39:348–357.
17. Cui JF. Identification and quantification of ginsenosides in various commercial ginseng preparations. *European journal of pharmaceutical sciences*, 1995, 3:77–85.
18. van Breemen RB et al. Electrospray liquid chromatography/mass spectrometry of ginsenosides. *Analytical chemistry*, 1995, 67:3985–3989.
19. Sprecher E. Ginseng: miracle drug or phytopharmacon? *Deutsche Apotheker Zeitung*, 1987, 9:52–61.
20. *British herbal pharmacopoeia.* London, British Herbal Medicine Association, 1990.
21. German Commission E Monograph, Ginseng radix. *Bundesanzeiger*, 1991, 11:17 January.
22. Hallstrom C, Fulder S, Carruthers M. Effect of ginseng on the performance of nurses on night duty. *Comparative medicine East and West*, 1982, 6:277–282.
23. D'Angelo L et al. Double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. *Journal of ethnopharmacology*, 1986, 16:15–22.
24. Pieralisi G, Ripari P, Vecchiet L. Effects of a standardized ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements on physical performance during exercise. *Clinical therapeutics*, 1991, 13:373–382.
25. Van Schepdael P. Les effets du ginseng G115 sur la capacité physique de sportifs d'endurance. *Acta therapeutica*, 1993, 19:337–347.
26. Forgo I, Kirchdorfer AM. The effect of different ginsenoside concentrations on physical work capacity. *Notabene medici*, 1982, 12:721–727.
27. Forgo I, Kirchdorfer AM. On the question of influencing the performance of top sportsmen by means of biologically active substances. *Ärztliche Praxis*, 1981, 33:1784–1786.

28. Forgo I. Effect of drugs on physical performance and hormone system of sportsmen. *Münchener Medizinische Wochenschrift*, 1983, 125:822–824.
29. Forgo I, Schimert G. The duration of effect of the standardized ginseng extract in healthy competitive athletes. *Notabene medici*, 1985, 15:636–640.
30. Wagner H, Norr H, Winterhoff H. Plant adaptogens. *Phytomedicine*, 1994, 1:63–76.
31. Sonnenborn U, Proppert Y. Ginseng (*Panax ginseng* C.A. Meyer). *British journal of phytotherapy*, 1991, 2:3–14.
32. Owen RT. Ginseng: A pharmacological profile. *Drugs of today*, 1981, 17:343–351.
33. Phillipson JD, Anderson LA. Ginseng-quality, safety and efficacy? *Pharmaceutical journal*, 1984, 232:161–165.
34. Takeda A, Yonezawa M, Katoh N. Restoration of radiation injury by ginseng. I. Responses of X-irradiated mice to ginseng extracts. *Journal of radiation research*, 1981, 22:323–335.
35. Yonezawa M, Katoh N, Takeda A. Restoration of radiation injury by ginseng. IV. Stimulation of recoveries in CFUs and megakaryocyte counts related to the prevention of occult blood appearance in X-irradiated mice. *Journal of radiation research*, 1985, 26:436–442.
36. Zhang JS et al. Modification of radiation response in mice by fractionated extracts of *Panax ginseng*. *Radiation research*, 1987, 112:156–163.
37. Qian BC et al. Effects of ginseng polysaccharides on tumor and immunological function in tumor-bearing mice. *Yao hsueh hsueh pao*, 1987, 8:277–280.
38. Yun TK, Yun YS, Han IW. An experimental study on tumor inhibitory effect of red ginseng in mice and rats exposed to various chemical carcinogens. In: *Proceedings of the third International Ginseng Symposium*. Seoul, Korean Ginseng Research Institute, 1980:87–113.
39. Choi CW, Lee SI, Huk K. Effect of ginseng on hepatic alcohol metabolizing enzyme system activity in chronic alcohol-treated mouse. *Korean journal of pharmacognosy*, 1984, 20:13–21.
40. Hikino H et al. Antihepatotoxic actions of ginsenosides from *Panax ginseng* roots. *Planta medica*, 1985, 51:62–64.
41. Nakagawa S et al. Cytoprotective activity of components of garlic, ginseng and ciwujia on hepatocyte injury induced by carbon tetrachloride in vitro. *Hiroshima journal of medical science*, 1985, 34:303–309.
42. Chen X et al. Protective effects of ginsenosides on anoxia/reoxygenation of cultured rat monocytes and on reperfusion injuries against lipid peroxidation. *Biomedica biochimica acta*, 1987, 46:646–649.
43. Lu G, Cheng XJ, Yuan WX. Protective action of ginseng root saponins on hypobaric hypoxia in animals. *Yao hsueh hsueh pao*, 1988, 9:391–394.
44. Banerjee U, Izquierdo JA. Anti-stress and antifatigue properties of *Panax ginseng*: Comparison with piracetam. *Acta physiologica et therapeutica Latinoamericana*, 1982, 32:277–285.

45. Cheng XJ et al. Protective effects of ginsenosides on anoxia/reoxygenation of cultured rat myocytes and on reperfusion injuries against lipid peroxidation. *Biomedica biochimica acta*, 1987, 46:646–649.
46. Saito H. Neuropharmacological studies on *Panax ginseng.* In: Chang HM et al., eds. *Advances in Chinese medicinal materials research.* Singapore, World Scientific Publishing, 1974:509–518.
47. Filaretov AA et al. Effect of adaptogens on the activity of the pituitary-adrenocortical system in rats. *Bulletin of experimental biology and medicine*, 1986, 101:627–629.
48. Lu G, Cheng XJ, Yuan WX. Effects of the ginseng root saponins on serum corticosterone and brain neurotransmitters of mice under hypobaric and hypoxic environment. *Yao hsueh hsueh pao*, 1988, 9:489–492.
49. Ng TB, Li WW, Yeung HW. Effects of ginsenosides, lectins, and *Momordica charantia* insulin-like peptides on corticosterone production by isolated rat adrenal cells. *Journal of ethnopharmacology*, 1987, 21:21–29.
50. Sonnenborn U. Ginseng-Nebenwirkungen: Fakten oder Vermutungen? *Medizinische Monatsschrift für Pharmazeuten*, 1989, 12:46–53.
51. Hiai S et al. Stimulation of pituitary-adrenocortical system by ginseng saponin. *Endocrinology Japan*, 1979, 26:661.
52. Hiai S, Sasaki S, Oura H. Effects of Ginseng saponin on rat adrenal cyclic AMP. *Planta medica*, 1979, 37:15–19.
53. Singh VK, Agarwal SS, Gupta BM. Immunomodulatory activity of *Panax ginseng* extract. *Planta medica*, 1984, 50:462–465.
54. Sonnenborn U. Ginseng-neuere Untersuchungen immunologischer, und endokrinologischer Aktivitäten einer alten Arzneipflanze. *Deutsche Apotheker Zeitung*, 1987, 125:2052–2055.
55. Fulder S. The growth of cultured human fibroblasts treated with hydrocortisone and extracts of the medicinal plant *Panax ginseng. Experimental gerontology*, 1977, 12:125–131.
56. Gupta S et al. A new mitogen and interferon inducer. *Clinical research*, 1980, 28:504A.
57. Singh VK, Agarwal SS, Gupta BM. Immunomodulatory effects of *Panax ginseng* extract. *Planta medica*, 1984, 50:459.
58. Jie YH, Cammisuli S, Baggiolini M. Immunomodulatory effects of *Panax ginseng* C. A. Meyer in the mouse. *Agents and actions*, 1984, 15:386–391.
59. Avakian EV et al. Effect of *Panax ginseng* on energy metabolism during exercise in rats. *Planta medica*, 1984, 50:151–154.
60. Brekhman II, Dardymov IV. Pharmacological investigation of glycosides from ginseng and *Eleutherococcus*. *Journal of natural products*, 1969, 32:46–51.
61. Hassan Samira MM et al. Effect of the standardized ginseng extract G 115 on the metabolism and electrical activity of the rabbit's brain. *Journal of international medical research*, 1985, 13:342–348.

62. Petkov V. Effect of ginseng on the brain biogenic monoamines and 3', 5'-AMP system. Experiments on rats. *Arzneimittel-Forschung*, 1978, 28:338–339.
63. Bombardelli E, Cristoni A, Lietti A. The effect of acute and chronic ginseng saponins treatment on adrenals function: biochemistry and pharmacological aspects. In: *Proceedings of the third International Ginseng Symposium*. Seoul, Korean Ginseng Research Institute, 1980:9–16.
64. Lewis WH, Zenger VE, Lynch RG. No adaptogen response of mice to ginseng and *Eleutherococcus* infusions. *Journal of ethnopharmacology*, 1983, 8:209–214.
65. Martinez B, Staba EJ. The physiological effects of *Aralia*, *Panax* and *Eleutherococcus* on exercised rats. *Japanese journal of pharmacology*, 1984, 35:79–85.
66. Liu CX, Xiao PG. Recent advances in ginseng research in China. *Journal of ethnopharmacology*, 1992, 36:27–38.
67. Yang ZW. Renshen. In: Chang HM, But PPH, eds., *Pharmacology and applications* of *Chinese materia medica*, Vol. 1. Singapore, World Scientific Publishing, 1986:17–31.
68. Han BH, Han YN, Park MH. Chemical and biochemical studies on antioxidant components of ginseng. In: Chang HM, Tso WW, Koo A. *Advances in Chinese medicinal materials research*. World Scientific Publishing, Singapore, 1985:485–498.
69. Kim H et al. Ginsenosides protect pulmonary vascular endothelium against radical-induced injury. *Biochemical and biophysical research communications*, 1992, 189:670–676.
70. Petkov VD et al. Memory effects of standardized extracts of *Panax ginseng* (G115), *Ginkgo biloba* (GK501) and their combination Gincosan (PHL00701). *Planta medica*, 1993, 59:106–114.
71. Huang KC. Herbs with multiple actions. In: *The pharmacology of Chinese herbs*. Boca Raton, FL, CRC Press, 1993:21–48.
72. Marles R, Farnsworth NR. Antidiabetic plants and their active constituents. *Phytomedicine*, 1995, 2:137–189.
73. Wang BX et al. Studies on the mechanism of ginseng polypeptide induced hypoglycemia. *Yao hsueh hsueh pao*, 1989, 25:727–731.
74. Davydov VV, Molokovsky A, Limarenko AY. Efficacy of ginseng drugs in experimental insulin-dependent diabetes and toxic hepatitis. *Patologichezkaia Fiziologiia I Eksperimentalkaia Terapiia*, 1990, 5:49–52.
75. Kim C. Influence of ginseng on mating behavior in male rats. *American journal of Chinese medicine*, 1976, 4:163–168.
76. Yamamoto M. Stimulatory effect of *Panax ginseng* principals on DNA and protein synthesis in rat testes. *Arzneimittel-Forschung*, 1977, 27:1404–1405.
77. Suzuki Y et al. Effects of tissue cultured ginseng on the function of the stomach and small intestine. *Yakugaku zasshi*, 1991, 111:765–769.

78. Suzuki Y et al. Effects of tissue cultured ginseng on gastric secretion and pepsin activity. *Yakugaku zasshi*, 1991, 111:770–774.
79. Matsuda H, Kubo M. Pharmacological study on *Panax ginseng* C.A. Meyer. II. Effect of red ginseng on the experimental gastric ulcer. *Yakugaku zasshi*, 1984, 104:449–453.
80. Hikino H. Antihepatotoxic activity of crude drugs. *Yakugaku zasshi*, 1985, 105:109–118.
81. Lin JH et al. Effects of ginseng on the blood chemistry profile of dexamethasone-treated male rats. *American journal of Chinese medicine*, 1995, 23:167–172.
82. Kumazawa N et al. Protective effects of various methanol extracts of crude drugs on experimental hepatic injury induced by carbon tetrachloride in rats. *Yakugaku zasshi*, 1990, 110:950–957.
83. Knapik JJ, Wright JE, Welch MJ. The influence of *Panax ginseng* on indices of substrate utilization during repeated, exhaustive exercise in man. *Federation proceedings*, 1983, 42:336.
84. Morris AC, Jacobs I, Kligerman TM. No ergogenic effect of ginseng extract after ingestion. *Medical science of sports exercise*, 1994, 26:S6.
85. Scaglione F et al. Immunomodulatory effects of two extracts of *Panax ginseng* C.A. Meyer. *Drugs*, *experimental and clinical research*, 1990, 26:537–542.
86. Kwan HJ, Wan JK. Clinical study of treatment of diabetes with powder of the steamed insam (ginseng) produced in Kaesong, Korea. *Technical information*, 1994, 6:33–35.
87. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. *Diabetes care*, 1995, 18:1373–1375.
88. Choi HK, Seong DW. Effectiveness for erectile dysfunction after the administration of Korean red ginseng. *Korean journal of ginseng science*, 1995, 19:17–21.
89. Bradley PR, ed. *British herbal compendium*, Vol. 1. Guildford UK, British Herbal Medicine Association, 1992:115–118.
90. Sonnenborn U, Hänsel R. *Panax ginseng*. In: De Smet PAGM et al., eds. *Adverse reactions of herbal drugs*. Springer-Verlag, Berlin, 1992:179–192.
91. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. *Journal of clinical psychopharmacology*, 1987, 7:201–202.
92. Shader RI, Greenblatt DJ. Phenelzine and the dream machine-ramblings and reflections. *Journal of clinical psychopharmacology*, 1985, 5:67.
93. Soldati F. Toxicological studies on ginseng. *Proceedings of the fourth International Ginseng Symposium*. Daejeon, Republic of Korea, Korean Ginseng and Tobacco Research Institute, 1984.
94. Siegel RK. Ginseng abuse syndrome: problems with the panacea. *Journal of the American Medical Association*, 1979, 241:1614–1615.

95. Tyler V. Performance and immune deficiencies. In: *Herbs of choice*. New York, Pharmaceutical Products Press, 1994:155–157.
96. Ryu SJ, Chien YY. Ginseng-associated cerebral arteritis. *Neurology*, 1995, 45:829– 830.
97. Lou BY et al. Eye symptoms due to ginseng poisoning. *Yen ko hsueh pao*, 1989, 5:96–97.
98. Palmer BV, Montgomery AC, Monteiro JC. Gin Seng and mastalgia. *British medical journal*, 1978, 279:1284.
99. Koriech OM. Ginseng and mastalgia. *British medical journal*, 1978, 297:1556.
100. Punnonen R, Lukola A. Oestrogen-like effect of ginseng. *British medical journal*, 1980, 281:1110.
101. Hopkins MP, Androff L, Benninghoff AS. Ginseng face cream and unexplained vaginal bleeding. *American journal of obstetrics and gynecology*, 1988, 159:1121–1122.
102. Buchi K, Jenny E. On the interference of the standardized ginseng extract G115 and pure ginsenosides with agonists of the progesterone receptor of the human myometrium. *Phytopharm*, 1984:1–6.
103. Forgo I, Kayasseh L, Staub JJ. Effect of a standardized ginseng extract on general well-being, reaction capacity, pulmonary function and gonadal hormones. *Medizinische Welt*, 1981, 19:751–756.
104. Reinhold E. Der Einsatz von Ginseng in der Gynäkologie. *Natur- und Ganzheits Medizin*, 1990, 4:131–134.

Radix Glycyrrhizae*

Definition

Radix Glycyrrhizae consists of the dried roots and rhizomes of *Glycyrrhiza glabra* L. and its varieties (*1–7*) or of *Glycyrrhiza uralensis* Fisch. (*6*, *7*) (Fabaceae).[1]

Synonyms

Liquiritae officinalis Moench is a synonym of *Glycyrrhiza glabra* L. (*1*).

Selected vernacular names

Glycyrrhiza glabra L. and its varieties

Adimaduram, akarmanis, asloosoos, aslussos, athimaduram, athimaduramu, athimathuram, bekh-e-mahak, bois doux, cha em thet, estamee, gancao, glycyrrhiza, herbe aux tanneurs, hsi-pan-ya-kan-tsao, irk al hiel, irk al hilou, irksos, jakyakgamcho-tang, jashtimadhu, jethimadh, jethimadha, kanpo, kanzo, kan-ts'ao, kum cho, Lakritzenwurzel, licorice, licorice root, liquiritiae radix, liquorice, liquorice root, madhuyashti, madhuyashti rasayama, mulathee, muleti, mulhatti, neekhiyu, Persian licorice, racine de reglisse, racine douce, reglisse, reglisse officinalis, rhizoma glycyrrhizae, Russian licorice, Russian liquorice, Russisches Süssholz, si-pei, sinkiang licorice, Spanish licorice, Spanish liquorice, Spanisches Süssholz, Süssholzwurzel, sweet root, sweetwood, ud al sus, velmi, walmee, welmii, xi-bei, yashti, yashtimadhu, yashtimadhukam, yashtomadhu (*1–15*).

Glycyrrhiza uralensis Fisch.

Chinese licorice, Chinese liquorice, gancao, kan-ts'ao, kanzo, kanzoh, licorice root, liquiritiae radix, north-eastern Chinese licorice, saihoku-kanzoh, tohoku kanzo, tongpei licorice, tung-pei-kan-tsao, Ural liquorice, uraru-kanzo (*14–17*).

---

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

[1] Glycyrrhiza inflata Bat. is listed in the Chinese pharmacopoeia (6). However, literature references to botanical, chemical, and biological studies on this species are rare. Therefore, it has not been included in this monograph.

Description

Glycyrrhiza glabra L. and its varieties

A perennial plant, up to more than 1m in height, erect, with highly developed stoloniferous roots. Leaves compound, 9–17 alternate imparipinnate leaflets, oblong to elliptical-lanceolate, acute or obtuse; racemes loose, shorter than the leaves or a little longer. Flowers 1 cm long. Flat pods oblong to linear, 1–3 cm long by 6 mm wide, more or less densely echinate glandular, many-seeded or abbreviated, 2- or 3-seeded (*1*, *11*).

Glycyrrhiza uralensis Fisch.

A perennial glandular herb, 30–100 cm high. Stem erect, with short whitish hairs and echinate glandular hairs; the lower part of the stem is woody. Leaves alternate, imparipinnate; leaflets 7–17, ovate-elliptical, 2–5.5 cm long by 1–3 cm wide; apex obtuse-rounded; base rounded; both surfaces covered with glandular hairs and short hairs. Stipules lanceolate. Inflorescence an axillary cluster. Flowers purplish, papilionaceous; calyx villous. Fruit a flat pod, oblong, sometimes falcate, 6–9 mm wide, densely covered with brownish echinate glandular hairs. Seeds 2–8. The root is cylindrical, fibrous, flexible, 20–22 cm long and 15 mm in diameter, with or without cork, cork reddish, furrowed, light yellow inside (*16*).

Plant material of interest: dried root and rhizome

General appearance

Glycyrrhiza glabra L. and its varieties

The commercial variety, *G. glabra* var. *typica* Regel & Herd, known as Spanish liquorice, consists generally of roots and rhizomes in nearly cylindrical pieces, up to 1 m long and 5–20 mm in diameter; externally, the bark is brownish grey to dark brown, longitudinally wrinkled, occasionally bearing small dark buds in rhizomes or small circular or transverse rootlet-scars in roots. The peeled root is yellow, smooth, fibrous, finely striated; fracture, fibrous in the bark and splintery in the wood; internally, bright yellow. A distinct cambium ring separates the yellowish grey bark from the finely radiate yellow wood; central pith, only in rhizomes (*1*, *2*, *7*).

The commercial variety, *G. glabra* var. *glandulifera* (Wald et Kit) Regel & Herd, known as Russian liquorice, consists mainly of roots, in cylindrical pieces somewhat tapering and sometimes longitudinally split; 15–40 cm long, 1–5 cm in diameter. The enlarged crown of the root may attain up to 10 cm in diameter; externally, the unpeeled root purplish brown, somewhat scaly, with stem scars at the top; the peeled root yellowish, coarsely striated; fracture as for Spanish type; internally, yellow, radiating (*1*).

Glycyrrhiza uralensis Fisch.

The roots and rhizomes are cylindrical, fibrous, flexible, 20–100 cm long, 0.6–3.5 cm in diameter, with or without cork. Externally reddish brown or greyish brown, longitudinally wrinkled, furrowed, lenticellate, and with sparse rootlet scars. Texture compact, fracture slightly fibrous, yellowish white, starchy; cambium ring distinct, rays radiate, some with clefts. Rhizomes cylindrical, externally with bud scars, pith present in the centre of fracture (*6*, *7*, *16*, *17*).

Organoleptic properties

Odour slight and characteristic (*1*, *6*, *7*); taste, very sweet (*1*, *6*, *7*, *13*, *15*, *17*).

Microscopic characteristics

In transverse section the cork is thick, brown or purplish brown, formed of several layers of flattened polygonal thin-walled cells; cortex of phelloderm in root somewhat narrow, yellow fibres of parenchyma cells contain isolated prisms of calcium oxalate; phloem, wide, yellow, traversed by numerous wavy parenchymatous medullary rays, 1–8 cells wide and consisting of numerous radial groups of fibres, each surrounded by a crystal sheath of parenchyma cells. Each cell usually contains a prism of calcium oxalate and layers of parenchyma alternating with sieve tissue, the latter occasionally obliterated, appearing as refractive irregular structures; phloem fibres, very long, with very narrow lumen and strongly thickened stratified walls which are cellulosic in the inner part of the phloem and slightly lignified in the outer; xylem, yellow, distinctly radiate; xylem rays, consisting of small pale yellow parenchyma, groups of fibres similar to those of the phloem but more lignified, and surrounded by crystal-sheath, tracheids, and large wide lumen vessels, 80–200 µm in diameter, with thick yellow reticulate walls or with numerous oval bordered pits with slit-shaped openings. Other parenchyma cells contain small round or oval starch granules. Pith, only in rhizome, dark yellow, parenchymatous. Root, with 4-arch primary xylem, no pith and shows 4 broad primary medullary rays, radiating from the centre at right angles to one another. In peeled liquorice, the cork, cortex, and sometimes part of the phloem are absent (*1*).

Powdered plant material

Light yellow in the peeled or brownish yellow or purplish brown in the unpeeled root. Characterized by the numerous fragments of the fibres accompanied by crystal-sheath, the fibres 8–25 µm, mostly 10–15 µm, in diameter; dark yellow fragments of vessels, 80–200 µm in diameter, containing solitary prismatic crystals of calcium oxalate, free or in cells 10–

35 µm (mostly 15–25 µm) long; numerous simple oval, round or fusiform starch granules, free or in parenchyma cells, with no striation but occasionally showing hilum, 2–20 µm (mostly about 10 µm) in diameter; cork may be present (*1*, *2*, *7*).

Geographical distribution

Glycyrrhiza glabra

Native to central and south-western Asia and the Mediterranean region (*11*, *12*, *13*). It is cultivated in the Mediterranean basin of Africa, in southern Europe, and in India (*1*, *11–13*).

Glycyrrhiza uralensis

Northern China, Mongolia, and Siberia (*16*, *17*).

General identity tests

Macroscopic, microscopic, and microchemical examinations (*1–7*); and thin-layer chromatographic analysis for the presence of glycyrrhizin (*2–7*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Glycyrrhizae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*18–20*). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*—not more than 10^2/g. Preparations for internal use: aerobic bacteria—not more than 10^5/g or ml; fungi—not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/g or ml; *Escherichia coli*—0/g or ml.

Total ash

Not more than 7% (*6*, *7*).

Acid-insoluble ash

Not more than 2% (*1–3*, *6*, *7*).

Sulfated ash

Not more than 10% (*2*).

Water-soluble extractive

Not less than 20% (*8*).

Dilute alcohol-soluble extractive

Not less than 25% (*7*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Glycyrrhizae is not more than 0.05 mg/kg (*20*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*18*) and guidelines for predicting dietary intake of pesticide residues (*21*).

Heavy metals

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*18*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*18*).

Other purity tests

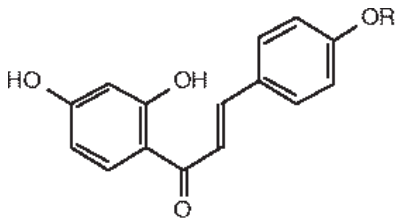
Alcohol-soluble extractive, chemical, and foreign organic matter tests to be established in accordance with national requirements.

Chemical assays

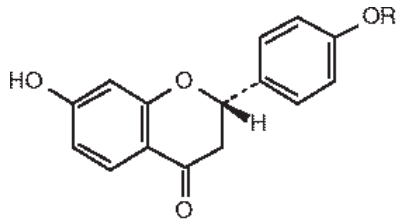
Assay for glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) content (at least 4%) by means of spectrophotometric (*1*, *2*), thin-layer chromatographic–densitometric (*22*, *23*) or high-performance liquid chromatographic methods (*24–26*).

Major chemical constituents

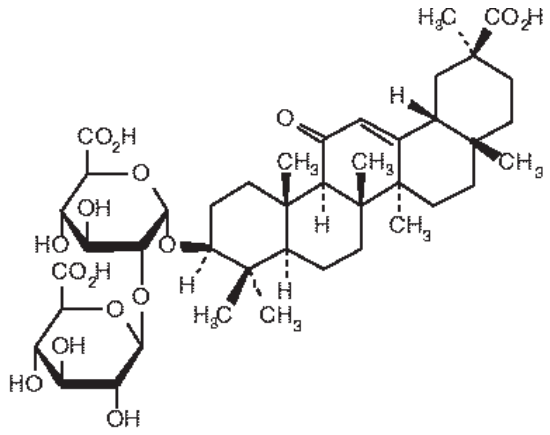
The major constituents are triterpene saponins. Glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) is the major component (2–9%); minor components occur in proportions that vary depending on the species and geographical location (*24–27*). Glycyrrhizin occurs as a mixture of potassium and calcium salts (*9*). It is a monodesmoside, which on hydrolysis releases two molecules of D-glucuronic acid and the aglycone glycyrrhetic (glycyrrhetinic) acid (enoxolone) (*28*). Glycyrrhizin is generally regarded as the active principle of Radix Glycyrrhizae and is responsible for its sweetness, which is 50 times that of sucrose (*27*). Flavonoid constituents include liquiritigenin and isoliquiritigenin.



isoliquiritigenin R = H
isoliquiritin R = β-D-glucopyranosyl



liquiritigenin R = H
liquiritin R = β-D-glucopyranosyl



glycyrrhizin or glycyrrhizic acid or glycyrrhizinic acid

aglycone = glycyrrhetic acid or glycyrrhetinic acid

Dosage forms

Crude plant material, dried extract and liquid extract. Store in a well-closed container, protected from light and moisture (*1*, *3*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

As a demulcent in the treatment of sore throats, and as an expectorant in the treatment of coughs and bronchial catarrh. Also in the prophylaxis and treatment of gastric and duodenal ulcers, and dyspepsia (*1*, *6*, *8*, *27–29*). As an anti-inflammatory agent in the treatment of allergic reactions (*27*), rheumatism and arthritis (*9*), to prevent liver toxicity, and to treat tuberculosis and adrenocorticoid insufficiency (*9*, *30*).

Uses described in folk medicine, not supported by experimental or clinical data

As a laxative, emmenagogue, contraceptive, galactagogue, antiasthmatic drug, and antiviral agent (*15*). In the treatment of dental caries, kidney stones, heart disease (*15*), "consumption", epilepsy, loss of appetite, appendicitis, dizziness, tetanus, diphtheria, snake bite, and haemorrhoids (*11*, *13*).

Pharmacology

Experimental pharmacology

The demulcent action of the drug is due primarily to glycyrrhizin (*27*). The antitussive and expectorant properties of the drug have also been attributed to glycyrrhizin, which accelerates tracheal mucus secretion (*27*).

The antiulcer activity of Radix Glycyrrhizae has been demonstrated both experimentally and clinically. Intraperitoneal, intraduodenal, or oral administration of aqueous or alcoholic extracts of Radix Glycyrrhizae reduced gastric secretions in rats, and it inhibited the formation of gastric ulcers induced by pyloric ligation, aspirin, and ibuprofen (*27*, *31–32*). Glycyrrhizin and its aglycone (glycyrrhetic acid, enoxolone), two of the active constituents of Radix Glycyrrhizae, both have antiphlogistic activity and increase the rate of mucus secretion by the gastric mucosa (*9*). Deglycyrrhizinated liquorice (97% of glycyrrhizin is removed) effectively treated stress-induced ulcers in animal models (*31–34*). The mechanism of antiulcer activity involves acceleration of mucin excretion through increasing the synthesis of glycoprotein at the gastric mucosa, prolonging the life of the epithelial cells, and antipepsin activity (*32*).

The spasmolytic activity of Radix Glycyrrhizae has been demonstrated in vivo (guinea-pig, rabbit, and dog) (*35–37*), and appears to be due to the flavonoids liquiritigenin and isoliquiritigenin (*38*).

Glycyrrhizin reduces the toxic action of carbon tetrachloride- and galactosamine-induced cytotoxicity in cultured rat hepatocytes, through its antioxidant activity (*9*, *27*). Glycyrrhizin inhibited histamine release from rat mast cells and prevented carbon tetrachloride-induced liver lesions and macrophage-mediated cytotoxicity (*27*). Intragastric administration of a flavonoid fraction isolated from Radix Glycyrrhizae to mice protected against carbon tetrachloride hepatotoxicity (*39*). Glycyrrhizin protected the liver apparently through its membrane stabilization effects (*27*).

The anti-inflammatory and antiallergic actions of the drug have been attributed to the corticosteroid-like activity of glycyrrhizin and glycyrrhetic acid (enoxolone). These compounds act indirectly by potentiating the activity of corticosteroids. In vitro, glycyrrhetic acid inhibits Δ^4β-reductase, an enzyme that competitively inactivates steroid hormones, and 11β-hydroxysteroid dehydrogenase, the enzyme that deactivates cortisol (*27*). Glycyrrhizin given intraperitoneally suppressed contact dermatitis in mice, and was more effective than prednisolone, but no effects were observed after oral administration (*9*).

In vitro, the drug inhibits the growth of *Bacillus subtilis (40)*, *Mycobacterium tuberculosis* (*41*), *Aspergillus spp. (42)*, *Staphylococcus aureus*, *Mycobacterium smegmatis*, and *Candida albicans* (*43*).

Clinical pharmacology

Oral administration of Radix Glycyrrhizae to 15 patients with peptic ulcer reduced symptoms and improved healing in 75% of the cases (*44*). Glycyrrhetic acid (enoxolone), the active constituent, produced its antiulcer activity by inhibiting 15-hydroxyprostaglandin dehydrogenase and Δ^{13}-prostaglandin reductase (*45*). Inhibition of these two enzymes stimulated an increase in the concentration of prostaglandins E and $F_{2\alpha}$ in the stomach, which promoted the healing of peptic ulcers owing to a cytoprotective effect on the gastric mucosa (*45*). Carbenoxolone, a derivative of glycyrrhetic acid, has been used clinically for years in the treatment of gastric and duodenal ulcers (*46*).

Oral administration of deglycyrrhizinated liquorice (380 mg, 3 times daily) to 169 patients with chronic duodenal ulcers was as effective as antacid or cimetidine treatments (*47*). These results indicate that, in addition to glycyrrhetic acid, other unidentified constituents of Radix Glycyrrhizae contribute to its antiulcer activity.

Reports on the usefulness of liquorice extracts on body fluid homeostasis in patients with Addison disease are contradictory. One study found no positive effects (*48*), while three other studies noted an increase in weight gain and sodium retention (*49–51*).

Contraindications

Radix Glycyrrhizae is contraindicated in patients with hypertension, cholestatic disorders or cirrhosis of the liver, hypokalaemia, or chronic renal insufficiency, and during pregnancy (*9*, *29*).

Warnings

Prolonged use of large doses (>50g/day) of the drug for extended periods (>6 weeks) may increase water accumulation, causing swelling of the hands and feet. Sodium excretion is reduced and potassium excretion is increased. Blood pressure may rise.

Precautions

General

Radix Glycyrrhizae should not be taken concurrently with corticosteroid treatment. If sore throat or cough persists for more than 3 days, the patient should consult a physician.

Drug interactions

Because it increases potassium loss, Radix Glycyrrhizae should not be administered for prolonged use with thiazide and loop diuretics or cardiac glycosides (*29*). Because it reduces sodium and water excretion, the effectiveness of drugs used in the treatment of hypertension may be reduced. Radix Glycyrrhizae should not be administered in conjunction with spironolactone or amiloride (*52*).

Carcinogenesis, mutagenesis, impairment of fertility

Radix Glycyrrhizae is not mutagenic in vitro (*53–55*).

Pregnancy: teratogenic effects

The drug is not teratogenic in animal models (*56*).

Pregnancy: non-teratogenic effects

The safety of Radix Glycyrrhizae preparations during pregnancy has not been established. As a precautionary measure the drug should not be used during pregnancy.

Nursing mothers

The safety of Radix Glycyrrhizae preparations during lactation has not been established. As a precautionary measure the drug should not be used during lactation except on medical advice.

Paediatric use
The safety and effectiveness of the drug in children have not been established.

Other precautions
No information available about drug and laboratory test interactions.

Adverse reactions
No adverse reactions have been associated with the drug when used within the recommended dosage and treatment period.

Prolonged use (>6 weeks) of excessive doses (>50 g/day) can lead to pseudoaldosteronism, which includes potassium depletion, sodium retention, oedema, hypertension, and weight gain (*9*, *57*, *58*). In rare cases, myoglobinuria and myopathy can occur (*59*).

Posology
Unless otherwise prescribed, average daily dose of crude plant material, 5–15 g, corresponding to 200–800 mg of glycyrrhizin. Doses of other preparations should be calculated accordingly (*29*). Radix Glycyrrhizae should not be used for longer than 4–6 weeks without medical advice.

References
1. *African pharmacopoeia*, *Vol. 1*, 1st ed. Lagos, Organization of African Unity, Scientific Technical & Research Commission, 1985:131–134.
2. *European pharmacopoeia*, 2nd ed. Strasbourg, Council of Europe, 1995.
3. *British pharmacopoeia*. London, Her Majesty's Stationery Office, 1988.
4. *Deutsches Arzneibuch 1996*. Stuttgart, Deutscher Apotheker Verlag, 1996.
5. *Pharmacopoeia Helvetica VII*. Berne, Département fédéral de l'intérieur, 1994.
6. *Pharmacopoeia of the People's Republic of China* (English ed.). Guangzhou, Guangdong Science and Technology Press, 1992.
7. *The pharmacopoeia of Japan XII*. Tokyo, The Society of Japanese Pharmacopoeia, 1991.
8. *Farmakope Indonesia*, 4th ed. Jakarta, Departemen Kesehatan, Republik Indonesia, 1995.
9. Bradley PR, ed. *British herbal compendium*, *Vol. 1*. Bournemouth, British Herbal Medicine Association, 1992:145–148.
10. Kapoor LD. *Handbook of Ayurvedic medicinal plants*. Boca Raton, FL, CRC Press, 1990:194–195.
11. *The Indian pharmaceutical codex. Vol. I. Indigenous drugs*. New Delhi, Council of Scientific & Industrial Research, 1953:112–113.
12. Ghazanfar SA. *Handbook of Arabian medicinal plants*. Boca Raton, FL, CRC Press, 1994:110–111.

13. Chin WY, Keng H. *An illustrated dictionary of Chinese medicinal herbs*. Singapore, CRCS Publications, 1992.
14. Hsu HY. *Oriental materia medica, a concise guide*. Long Beach, CA, Oriental Healing Arts Institute, 1986:532–535.
15. Farnsworth NR, ed. *NAPRALERT database*. University of Illinois at Chicago, IL, August 21, 1995 production (an on-line database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
16. *Medicinal plants in China*. Manila, World Health Organization, 1989 (WHO Regional Publications, Western Pacific Series, No. 2).
17. Keys JD. *Chinese herbs, their botany, chemistry and pharmacodynamics*. Rutland, VT, CE Tuttle, 1976:120–121.
18. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
19. *Deutsches Arzneibuch 1996. Vol. 2. Methoden der Biologie*. Stuttgart, Deutscher Apotheker Verlag, 1996.
20. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1997.
21. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (unpublished document WHO/FSF/FOS/97.7).
22. Takino Y et al. Quantitative determination of glycyrrhizic acid in liquorice roots by TLC-densitometry studies on the evaluation of crude drugs. VI. *Planta medica*, 1979, 36:74–78.
23. Vanhaelen M, Vanhaelen-Fastré R. Quantitative determination of biologically active constituents in medicinal plant crude extracts by thin-layer chromatography densitometry. *Journal of chromatography*, 1983, 281: 263–271.
24. Sticher O, Soldati F. Glycyrrhizinsäure-Bestimmung in Radix Liquiritiae mit Hochleistungs-flüssigkeitschromatographie (HPLC). *Pharmaceutica acta Helvetica*, 1978, 53:46–52.
25. Sagara K. Determination of glycyrrhizin in pharmaceutical preparations by ion-pair high-performance liquid chromatography. *Shoyakugaku zasshi*, 1986, 40:77–83.
26. Okada K et al. High-speed liquid chromatographic analysis of constituents in licorice root. I. Determination of glycyrrhizin. *Yakugaku zasshi*, 1981, 101:822–828.
27. Hikino H. Recent research on Oriental medicinal plants. In: Wagner H, Hikino H, Farnsworth NR, eds. *Economic and medicinal plant research.* Vol. 1. London, Academic Press, 1985:53–85.
28. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995:549–554.
29. German Commission E Monograph, Liquiritiae radix. *Bundesanzeiger*, 1985, 90:15 May.

30. Schambelan M. Licorice ingestion and blood pressure regulating hormones. *Steroids*, 1994, 59:127–130.
31. Dehpour AR et al. The protective effect of liquorice components and their derivatives against gastric ulcer induced by aspirin in rats. *Journal of pharmacy and pharmacology*, 1994, 46:148–149.
32. Dehpour AR et al. Antiulcer activities of liquorice and its derivatives in experimental gastric lesion induced by ibuprofen in rats. *International journal of pharmaceutics*, 1995, 119:133–138.
33. Morgan RJ et al. The protective effect of deglycyrrhinized liquorice against aspirin and aspirin plus bile acid-induced gastric mucosal damage, and its influence on aspirin absorption in rats. *Journal of pharmacy and pharmacology*, 1983, 35:605–607.
34. Russell RI, Morgan RJ, Nelson LM. Studies on the protective effect of deglycyrrhinized liquorice against aspirin (ASA) and ASA plus bile acid-induced gastric mucosal damage, and ASA absorption in rats. *Scandinavian journal of gastroenterology*, 1984, 19(Suppl.):97–100.
35. Takagi K, Harada M. Pharmacological studies on herb Peony root. III. Effects of peoniflorin on circulatory and respiration system and isolated organs. *Yakugaku zasshi*, 1969, 89:893–896.
36. Wrocinski T. Determination of the activity of spasmolytic drugs with reference to the papaverine standard. *Biuletyn Instytutu Roslin Leczniczych*, 1960, 6:236.
37. Shihata M, Elghamry MI. Experimental studies in the effect of *Glycyrrhiza glabra. Planta medica*, 1963, 11:37.
38. Chandler RF. Licorice, more than just a flavour. *Canadian pharmaceutical journal*, 1985, 118:420–424.
39. Wang GS, Han ZW. The protective action of *Glycyrrhiza* flavonoids against tetrachloride hepatotoxicity in mice. *Yao hsueh hsueh pao*, 1993, 28:572–576.
40. Sabahi T et al. Screening of plants from the southeast of Iran for antimicrobial activity. *International journal of crude drug research*, 1987, 25:72–76.
41. Grange JM, Davey RW. Detection of antituberculous activity in plant extracts. *Journal of applied bacteriology*, 1990, 68:587–591.
42. Toanun C, Sommart T, Rakvidhyasastra V. Effect of some medicinal plants and spices on growth of *Aspergillus*. *Proceedings of the 11th Conference of Science and Technology*. Bangkok, Kasetsart University, 1985:364–365.
43. Mitscher LA et al. Antimicrobial agents from higher plants. Antimicrobial isoflavonoids and related substances from *Glycyrrhiza glabra* L. var. *typica*. *Journal of natural products*, 1980, 43:259–269.
44. Chaturvedi GN. Some clinical and experimental studies on whole root of *Glycyrrhiza glabra* L. (Yashtimadhu) in peptic ulcer. *Indian medical gazette*, 1979, 113:200–205.
45. Baker ME, Fanestil DD. Liquorice as a regulator of steroid and prostaglandin metabolism. *Lancet*, 1991, 337:428–429.

46. Rask-Madsen J et al. Effect of carbenoxolone on gastric prostaglandin E2 levels in patients with peptic ulcer disease following vagal and pentagastrin stimulation. *European journal of clinical investigation*, 1983, 13:875–884.
47. Kassir ZA. Endoscopic controlled trial of four drug regimens in the treatment of chronic duodenal ulceration. *Irish medical journal*, 1985, 78:153–156.
48. Molhuysen JA et al. A liquorice extract with deoxycortone-like action. *Lancet*, 1950, ii:381–386.
49. Groen J et al. Extract of licorice for the treatment of Addison's disease. *New England journal of medicine*, 1951, 244:471–475.
50. Card WI et al. Effects of liquorice and its derivatives on salt and water metabolism. *Lancet*, 1953, i:663–667.
51. Groen J et al. Effect of glycyrrhizinic acid on the electrolyte metabolism in Addison's disease. *Journal of clinical investigation*, 1952, 31:87–91.
52. Doll R. Treatment of gastric ulcer with carbenoxolone: antagonistic effect of spironolactone. *Gut*, 1968, 9:42–45.
53. Sakai Y et al. Effects of medicinal plant extracts from Chinese herbal medicines on the mutagenic activity of benzo[a]pyrene. *Mutation research*, 1988, 206:327–334.
54. Lee HK et al. Effect of bacterial growth-inhibiting ingredients on the Ames mutagenicity of medicinal herbs. *Mutation research*, 1987, 192:99–104.
55. Yamamoto H, Mizutani T, Nomura H. Studies on the mutagenicity of crude drug extracts. I. *Yakugaku zasshi*, 1982, 102:596–601.
56. Leslie GB, Salmon G. Repeated dose toxicity studies and reproductive studies on nine Bio-Strath herbal remedies. *Swiss medicine*, 1979, 1:1–3.
57. Epistein MT et al. Effects of eating liquorice on the renin-angiotensin aldosterone axis in normal subjects. *British medical journal*, 1977, 1:488–490.
58. Stewart PM et al. Mineralocorticoid activity of liquorice: 11-β hydroxysteroid dehydrogenase deficiency comes of age. *Lancet*, 1987, ii:821–824.
59. Caradonna P et al. Acute myopathy associated with chronic licorice ingestion: Reversible loss of myoadenylate deaminase activity. *Ultrastructural pathology*, 1992, 16:529–535.

Flos Helichrysi arenarii

Definition

Flos Helichrysi arenarii consists of the dried inflorescences of *Helichrysum arenarium* (L.) Moench (Asteraceae) collected during the budding phase (*1*, *2*).

Synonyms

Antennaria arenarium L., Gnaphalium arenarium L. (*3*, *4*).

Selected vernacular names

Bessmertnik pestshan'i, bonässla, common shrubby everlasting, elicriso, eternal flower, everlasting, evighetsblomster, dwarf everlasting, fleur de pied de chat, flores gnaphalii arenerii, gyllene kattfötter, Fuhrmannsröschen, goldilocks, harilik käokuld, harnblumen, hietaolkikukka, immortelle, kaķpēdiņa dzeltenā, Katzenpfötchenblüten, kumlok buznitshi, mottenkrautblume, olmezcicek, rainblume, ruhr herb, ruhrkraut, sandgoldblume, sandimmortelle, sand-strohblume, sandy everlasting, sandy immortelles, siminoc, stoechados flos, strawflower, strobloem, Strohblume, suhotsvet, tsmin, yellow chaste weed, yellow chasteweed, yellow immortelle, zolotistka, zoloto solnetshnoje (*4–13*).

Geographical distribution

Indigenous to central, eastern, and southern Europe, the plant is both collected in the wild and cultivated commercially. The plant also grows in North America. In the Newly Independent States, it is found mainly in the European regions, but it is also grown in central Asia and west Siberia. The main suppliers are the former USSR, Poland and Turkey (*5*, *7*, *14*, *15*).

Description

A perennial herb, 10–30(60) cm high. Rhizome: short, strong, obliquely descendent, from 1–4 to 5–7(15) mm in diameter. Stems: fertile and sterile, erect, unbranched, eglandulous, grey, adpressed-tomentose. Leaves: alternate, grey-tomentose like the stems; basal leaves petiolate, linear-oblanceolate to spatulate, 7–60 mm long, 2–8 mm wide; stem leaves ses-

sile, lanceolate, narrowing to linear above, sometimes with crisply undulate margins. The leaves of sterile stems are oblong-spatulate, oblong-elliptic, restricted to the petiole. Inflorescence: capitula, numerous, globose, 3–6(9) mm in diameter; 10–30(100) capitula grouped in false umbels. Phyllaries, about 50, in 4–6(7) rows, membranous, flat or cucullate, yellow or yellowish-orange; inner ones oblong-spatulate to linear, outer ones obovate or elliptical, hairy. Flowers: hermaphrodite, tubular or tubular-infundibulate; corolla orange; pappus of about 30 yellowish-white hairs, as long as the corolla; pollinated by insects. Fruit: achene, pentagonal, oblong, brown, 0.7–1.2 mm long, with a pappus (*3*, *5*, *14*, *16–18*).

Plant material of interest: dried flower heads

General appearance

Flower heads in budding phase or at the beginning of flowering phase, spherical, about 7–9 mm in diameter, yellow, solitary or in groups, tangled together into false umbels. The receptacles are glabrous; the peduncles are woolly-pubescent, up to 1 cm long. The involucral bracts are somewhat spreading, characteristic, straw-like, shiny, imbricate, lemon-yellow in colour; outer bracts are ovate, middle ones are oblong-spatulate, inner ones are narrow, linear. The bracts enclose the tubular and ligulate flowers. The tubular flowers are small, orange-yellow, with a light yellow pappus. The ligulate florets are usually absent or inconspicuous (*1*, *5*).

Organoleptic properties

Odour: slightly aromatic; taste: slightly bitter, spicy and aromatic (*1*, *5*).

Microscopic characteristics

The bracts epidermis with oblong spongiose cells. The narrow parts of the bracts and the peduncle are covered by numerous, long, slender covering trichomes having few short basal cells and a long terminal cell; glandular trichomes characteristic of the Asteraceae family, with 8–12 cells, each pair of cells superposed on two others. Ovary, oval with unicellular club-shaped glandular trichomes and pappus hairs. Corolla with numerous glandular trichomes having a 12–14-cellular stalk and unicellular head (*1*, *5*).

Powdered plant material

No information available.

General identity tests

Macroscopic and microscopic examinations, chemical analysis and thin-layer chromatography tests for flavonoids, which are the characteristic constituents (*1*, *2*, *5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*19*).

Chemical

The thin-layer chromatogram must not show an orange zone above the brownish main zone (purity test for other *Helichrysum* species) (*2*).

Foreign organic matter

Foreign organic matter not more than 0.5%. Maximum 5% of flower heads with long flower stalks greater than 1 cm. Not more than 5% of broken flower heads, with a diameter less than 2 mm (*1*). Absence of *Helichrysum angustifolium* DC and *H. stoechas* flower heads as adulterants (*5*). Foreign matter, not more than 2% (*2*, *20*); absence of *H. italicum* (Roth) Guss. and *H. stoechas* flower heads (*20*).

Total ash

Not more than 8% (*1*). Not more than 7% (*2*).

Acid-insoluble ash

No information available.

Sulfated ash

Not more than 8.5% (*20*).

Water-soluble extractive

No information available.

Alcohol-soluble extractive

No information available.

Loss on drying

Not more than 12% (*1*). Not more than 10% (*21*).

Pesticide residues

The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*22*). For other pesticides, see the *European pharmacopoeia* (*22*) and the WHO guidelines on quality control methods for medicinal plant materials (*19*) and pesticide residues (*23*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*19*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*19*) for the analysis of radioactive isotopes.

Other purity tests

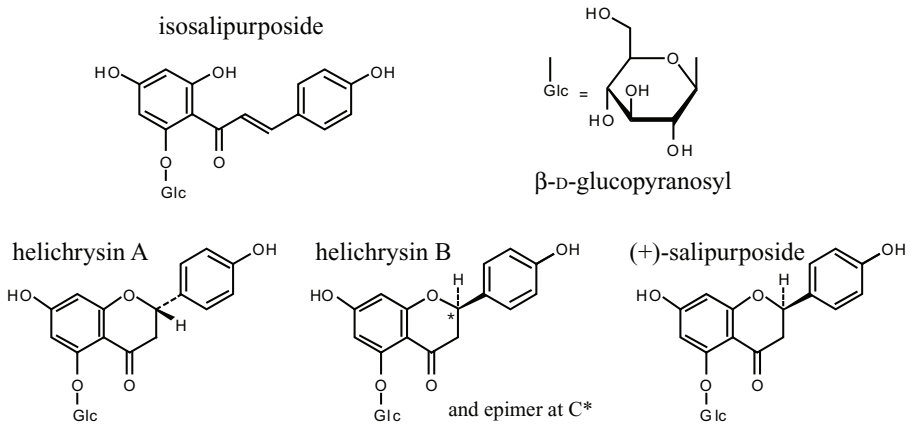
Content of mineral matter not more than 0.5% (*1*). Tests for acid-insoluble ash, alcohol-soluble extractive and water-soluble extractive to be established in accordance with national requirements.

Chemical assays

Contains not less than 6% of total flavonoids, expressed as isosalipurposide (*1*). Flavonoids, not less than 0.5% calculated as quercetin (*5, 21*). Flavonoids, not less than 0.6% calculated as hyperoside (*2*).

Major chemical constituents

The major constituents of the inflorescences are flavonoids: isosalipurposide (approximately 0.4% and pyranone derivatives responsible for the yellow colour of the involucral bracts), naringenin and its 5-*O*-diglucoside, helichrysin A (salipurposide) and helichrysin B, kaempferol glucosides, apigenin and its 7-*O*-glucoside, luteolin-7-*O*-glucoside, quercetin-3-*O*-glucoside and 3,5-dihydroxy-6,7,8-trimethoxyflavone. Also present are essential oil (approximately 0.05%; β-caryophyllene, heneicosane, linalool, α-terpineol, anethol, thymol, carvacrol and others), phthalides (5-methoxy-7-hydroxy-phthalide and its monoglucoside), coumarins (scopoletin, umbelliferone, aesculetin), pyranone derivatives (the yellow-coloured arenol and homoarenol), sterols (campesterol, β-sitosterol), caffeic acid derivatives, polysaccharides, carotenoids, tannins (*3*, *5*, *15*, *24–29*). The structures of the major constituents are presented below.



Medicinal uses

Uses supported by clinical data

No information was found.

Uses described in pharmacopoeias and well established documents

Flowers of *Helichrysum arenarium* are used for the treatment of dyspeptic disorders (*30*).

Uses described in traditional medicine

Helichrysum arenarium has been known in Europe as a medicinal plant for its choleretic, hepatoprotective and detoxifying activities (*27*, *31*). In traditional medicine, the drug is also employed as a diuretic. The flowers contain antibacterial constituents and bitter substances, which may also promote gastric and pancreatic secretion (*32*). Used as a mild spasmolytic and as an adjuvant in the treatment of chronic cholecystitis and cramp-like gall-bladder and biliary duct disorders, and peptic discomfort (*5*, *33*). It is also indicated for indigestion as well as for loss of appetite (*34–36*).

Pharmacology

Experimental pharmacology

Radical scavenging and antihyperlipidaemic effects

Methanol extracts of *Helichrysum* species were screened in vitro for antioxidant activity by two complementary test systems (2,2-diphenyl-1-pic-

rylhydrazyl radical (DPPH) free radical-scavenging and β-carotene/linoleic acid). In the first test system, the extracts showed no antioxidant activity. In the second test system, inhibition rates of the oxidation of linoleic acid were comparable to those of the synthetic antioxidant butylated hydroxytoluene (96%). It could be useful to consider use of the extract as an alternative antioxidant for the food processing industries (*37*).

The antioxidant properties of lyophilized water extracts from the dried inflorescences of *Helichrysum arenarium* with different polyphenol and flavonoid contents were examined in microsomal fractions of rat liver. Enzymatically-induced lipid peroxidation and nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome C-reductase activity in liver microsomes were measured by a spectrophotometric method. The extracts have weak DPPH free radical scavenging activity in microsomal fractions of rat liver at a concentration of 1 µg/ml measured by a chemiluminometric method. The activity was comparable to that of the flavonoid silibinin, the main constituent of *Silybium marianum* (*31*). Lyophilized water extracts of Flos Helichrysi diminished the enzymatically induced lipid peroxidation and reduced cytochrome C in a concentration-dependent manner. The same extracts inhibited NADPH-induced lipid peroxide formation at a concentration of 20 µg/ml and stimulated NADPH cytochrome C reductase in rat liver microsomes at a concentration of 100 µg/ml. The extracts were observed to be more effective than silibinin at the concentrations tested (*38*).

A methanolic extract obtained from inflorescences of *Helichrysum arenarium* was evaporated and the dry residue was dissolved in hot water. The solution was stored at 4 °C and the precipitate discarded. The remaining solution was divided into three aliquots a, b and c. Part a was extracted with ethyl acetate to obtain extract A, part b was extracted with diethyl ether to obtain extract B and part c was subjected to alkaline hydrolysis and then extracted with diethyl ether to obtain extract C. After evaporation, the dry residues A, B and C were further investigated for phenolic compound content by thin-layer chromatography and high-performance liquid chromatography (HPLC), as well as for 2,2-diphenyl-1-picrylhydrazyl-antiradical activity. Residue C exhibited stronger antiradical properties than non-hydrolysed residues A and B. HPLC analysis showed a greater increase in the strong antioxidant, caffeic acid, in residue C, resulting in an increase in the antiradical activity observed with residue C (*39*).

Antimicrobial activity

A 95% ethanol extract of the dried flowers and leaves of the plant was found to have weak antibacterial activity against *Pseudomonas aerugi-*

nosa at a concentration of 1mg/ml/agar plate. No activity was exhibited against *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella paratyphi* A, *Salmonella typhi*, *Shigella flexneri* and *Staphylococcus albus* and *Staphylococcus aureus*, at the same concentration (*40*). Fractionation of the dichloromethane extract of Flos Helichrysi yielded seven isolates, which exhibited varying antimicrobial activity against Gram-positive bacteria (*41*).

A 10% aqueous extract of the dried flowers of the plant demonstrated antiviral activity against herpes virus (type 2), influenza virus A2 (Manheim 57) and Vaccini virus, and was inactive against poliovirus type II in cell culture (*42*, *43*).

Spasmolytic activity

Aqueous solutions of the active constituents of the plant, naringenin-5-glucoside (I), kaempferol-3-glucoside (II) and apigenin, dissolved in phosphate-buffered sodium hydroxide (III) were intravenously injected at a dose of 4 mg/100 g body weight (bw) in rats. All preparations showed spasmolytic activity and had similar choleretic effects in rats (approximately 33% of that of dehydrocholic acid). This activity was highest following treatment with extract III, lower for II and least for I. Similar pharmacological tests were carried out with 5-methoxy-7-hydroxyphthalide isolated from the plant, but the results were negative. An alcohol extract containing all flavonoids and an aqueous extract containing no flavonoids (50 mg/100 g bw) were also tested. The extract with all flavonoids demonstrated spasmolytic activity similar to that of preparations I, II and III. The extract containing no flavonoids elicited a spastic response in smooth muscles isolated from rat intestine and gall-bladder. The researchers concluded that the activity of Galenical preparations of *Helichrysum arenarium* depended only on the flavonoid content. Infusions and decoctions (10%) of *Helichrysum arenarium* showed a rather weak spasmolytic effect (*44*).

Diuretic activity

No diuretic activity was observed when a decoction, infusion and various extracts (ether, ethanol, aqueous) of the dried whole plant were administered by the intraduodenal route to dogs and the intragastric route to rats at a dose of 10 mg/kg bw and 50 mg/kg bw, respectively. A parallel pharmacokinetic study in dogs showed poor absorption of the decoction from the gastrointestinal tract. An intravenous injection of the same doses of the drug to dogs had a significant diuretic effect (*44*).

Hypotensive activity
Intravenous injection of ethanol, aqueous and ether extracts of dried whole plant to dogs and rats at doses of 50 mg/kg and 500 mg/kg bw, respectively, produced a hypotensive effect (*44*).

Cytotoxic activity
A 10% aqueous extract of the dried flowers of the plant was inactive against HeLa cells in cell culture (*43*).

Clinical pharmacology
No information was found.

Adverse reactions
No information was found.

Contraindications
Due to the bile-stimulating effect of the drug, it should not be administered when there is obstruction of the bile ducts due to gallstones. It should only be used in patients with gallstones after consultation with a physician (*30*, *45*).

Precautions

General
Increased health risks or adverse effects following the correct administration of *Helichrysum arenarium* at therapeutic dosages have not been recorded, however chronic use may cause development of bile congestion (*46*).

Drug interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
No information was found.

Nursing mothers
No information was found.

Paediatric use

No information was found.

Dosage forms

Comminuted herb for teas and other Galenical preparations for internal use (*30*).

Posology

(Unless otherwise indicated)

The average daily dosage is 3 g of the drug or equivalent preparations (*30*).

Internal use. Infusion: one tablespoonful of the infusion (prepared by adding flowers to 200 ml of boiling water and infusing for 15 minutes), three times daily 20–40 minutes before meals (*47*). Decoction: one tablespoonful of a decoction (prepared by adding 10 g of cut flowers to 200 ml of boiling water and infusing for 30 minutes), three times daily before meals (*47*). Dry extract: granulated powder from the flowers, 1 g three times daily for 23 weeks (*48*).

References

1. *USSR pharmacopoeia*, 11th ed. *Vol. 2*. Moscow, Meditsina, 1990.
2. *Deutscher Arzneimittel-Codex – German pharmaceutical codex: a supplementary pharmacopoeia to the European and German Pharmacopoeia.* Berlin, Federal Union of German Associations of Pharmacists, 2005.
3. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific, 1994.
4. *Henriette's plant name search* (http://www.henriettesherbal.com/php/index.php).
5. Bisset NG, ed. *Herbal drugs and phytopharmaceuticals*, 2nd ed. Stuttgart, Medpharm Scientific Publishers, 2001.
6. Fleming T, ed. *Physician's desk reference (PDR) for herbal medicines*, 1st ed. Montvale, Medical Economics, 1998.
7. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific Publishers, 2001.
8. Kerbabajev BB. *Narodn'je I nautshn'je Turksmenskije nazvanija rasteni.* Ashabat, 'l'm, 1992.
9. Krall H et al. *Eesti Taimede Määraja.* Tartu, Eesti Loodusfoto, 1999.
10. Grigorescu E, Ciulei I, Ursula S. *Index fitoterapeutic.* Bucharest, Editura Medicala, 1986.
11. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
12. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Turku, Celsius Healthcare, 2006.

13. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005 (http://www.napralert.org).
14. Zadorozhnyi AM et al. *Spravotchnik po lekarstvennim rastenijam*. Moscow, Lesnaja promyshlennost', 1988.
15. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
16. Comarov VL, Shishkin BK. *Flora SSSR. Vol. 25.* Pod red. Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1959.
17. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR.* Izd. Moscow, Mysli, 1976.
18. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR.* 3-ie izd. Kishinev, Shtiintsa, 1986.
19. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
20. *Pharmacopoeia Helvetica,* 4 volumes. 7th ed. Berne, Département fédéral de l'intérieur, 1987.
21. Brown D. *Encyclopedia of herbs and their uses*. London, Dorling Kindersley, 1995.
22. *European Pharmacopoeia*, 5th ed. Strasbourg, Council of Europe, 2005.
23. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
24. Jakovlev GP, Blinova KF., eds. *Lekarstvennoje rastitel'noe syr'je. Farmakognozija.* St. Petersburg, SpetzxLit, 2004.
25. Judzentiene A, Butkiene R. Chemical composition of the essential oils of wild *Helichrysum arenarium* (L.) with differently colored inflorescences from eastern Lithuania. *Journal of Essential Oil Research*, 2006, 18:80–83.
26. Lemberkovics E et al. New data on composition of essential oil from inflorescence of everlasting (*Helichrysum arenarium* (L.) Moench.). *Acta Pharmaceutica Hungarica*, 2001, 71:187–191.
27. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Vol. 7*. Leningrad, Nauka, 1993.
28. Czinner E et al. Phytochemical study of phenolic compounds from Helichrysi flos by LC-DAD-MS. In: *Proceedings of the Phytochemical Society of Europe*, 2002, 47:99–109.
29. Vrkoc J. Structure of arenol and homoarenol, α-pyrone derivatives from *Helichrysum arenarium. Tetrahedron Letters*, 1971, 3:247–250.
30. Blumenthal M et al, eds. *The complete German Commission E monographs. Therapeutic guide to herbal medicines*. Austin, TX, American Botanical Council, 1998.
31. Czinner E et al. *In vitro* antioxidant properties of *Helichrysum arenarium* (l.) Moench. *Journal of Ethnopharmacology*, 2000, 73:437–443.

32. Amirdowlat Amasyaci. *Nenuzhnoe dlja neuczej* (*Needless for ignoramus*). Naucznoe nasledstvo. Moscow, Nauka, 1990.
33. Petkov V, ed. *Sovremennaja fitoterapija*. Sofia, Meditsina i fizkultura, 1988.
34. Muravjova DA. *Farmakognozija*. Moscow, Meditsina, 1978.
35. Turova AD, Sapozhnikova EN. *Lekarstvennie rastenija SSSR i ikh primenenie*. Moscow, Meditsina, 1982.
36. Yakovlev GP, Blinova KF, eds. *Rastenija dlja nas*. St. Petersburg, Utchebnaja kniga, 1996.
37. Tepe B et al. In vitro antioxidant activities of the methanol extracts of four Helichrysum species from Turkey. *Food Chemistry*, 2004, 90:685–689.
38. Czinner E et al. The *in vitro* effect of Helichrysi flos on microsomal lipid peroxidation. *Journal of Ethnopharmacology*, 2001, 77:31–35.
39. Sroka Z et al. Antiradical activity of hydrolyzed and non-hydrolyzed extracts from Helichrysi inflorescentia and its phenolic contents. *Zeitschrift für Naturforschung*, 2004, 59:363–367.
40. Cosar G, Cubukcu B. Antibacterial activity of Helichrysum species growing in Turkey. *Fitoterapia*, 1990, 61:161–164.
41. Rios JL, Recio MC, Villar A. Isolation and identification of the antibacterial compounds from Helichrysum stoechas. *Journal of Ethnopharmacology*, 1991, 33:51–55.
42. Kaij-A-Kamb M, Amoros M, Girre L. Search for new antiviral agents of plant origin. *Pharmaceutica Acta Helvetica*, 1992, 67:130–147.
43. May G, Willuhn G. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. *Arzneimittel-Forschung*, 1978, 28:1–7.
44. Szadowska A. Pharmacology of galenic preparations and flavonoids isolated from Helichrysum arenarium. *Acta Polonica Pharm*, 1962, 19:465–479.
45. Fleming T, ed. *Physicians, desk reference (PDR) for herbal medicines*. Montvale, Medical Economics Company, 2000.
46. Lager AA. *Fitoterapija*. Krasnojarsk, Izdatel'stvo krasnojarskogo universiteta, 1988.
47. Kukes VG, ed. *Fitoterapija s osnovami klinitczeskoj farmakologii*. Moscow, Meditsina, 1999.
48. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.

Fructus Hippophaës recens

Definition

Fructus Hippophaës recens consists of the ripe, fresh fruits of *Hippophaë rhamnoides* L. (Elaeagnaceae) (*1*, *2*).

Synonyms

Argussiera rhamnoides (L.) Bubani, *Elaeagnus rhamnoides* (L.), A. Nelson, *Hippophaës rhamnoideum* St.-Lag., *H. angustifolia* Lodd. ex Dippel, *H. rhamnoidea* St.-Lag. in Cariot, *H. salicifolia* D. Don, *H. sibirica* Lodd., *H. stourdziana* J. Szabó, *H. taurica* hort. ex Dippel, *H. tibetana* Schlecht, *Osyris rhamnoides* Scop., *Rhamnoides hippophaë* Moench (*3–5*).

Selected vernacular names

Abm, argasse, argousier, argoussier, astelpaju, bautphut, buckthorn, cătină, cătină albă, chharma, ch-liu, chuk, chuma, dhurchuk, duindoorn, echter sanddorn, espino armarillo, espino falso, ghâ, gorra, griset, haftdorn, kaham, kalabisa, kâm, kando, milech, miles, neichak, oblebiha krushinovidnaja, olivella spinosa, pangi, sallow thorn, sanddorn, sarla, scheitbeziën, sea berry, sea buckthorn, seedorn, sendjed-e-talkh, shallow thorn, shawk el qassâr, sirma, sirna, smiltsērkšķis, starbu, stechdorn, stranddorn, sûl rûmi, suts, olivella, olivello spinoso, rakytnik řešetlákový, rakytnik rešetliakovitý, ramnoida hiopogeo, tarru, tarwa, tasru, tirku, tsakanda, tsarap, tsarmand, tsarmaniechak, tserkar, tswak, tyrni, vetrice spinosa, weidendorn, willow thorn, yabani igde ağ, zhongguoshaji (*4*, *6–18*).

Geographical distribution

Indigenous to Europe and some northern regions of Asia, it is widely distributed throughout the temperate regions of Asian countries. In the Newly Independent States, it is grown in the Caucasus and the Ural Federal District, in southern Siberia, and also in Altai and the Sayan Mountains. It is domesticated in various parts of the world (*4*, *9*, *19–26*).

Description

Shrub or small tree, deciduous, thorny, 1.5–5(10) m tall, with a lifespan of 5–20 years. Extensive root system with nitrogen-fixing nodules. Stems, many stout branches, round greyish-green crown, brown or black rough bark, thorny grey twigs. Leaves, alternate, almost sessile, linear to lanceolate, enrolled margins, dark green on the upper surface, silver-grey on the lower surface, main central vein prominent, 2–8 cm long, up to 8 mm wide. Dioecious, anemophilous. Flowers, unisexual; male flowers in catkin-like spikes, 2-sepalled calyx, brown-spotted ovate sepals, 4 stamens and no corolla; female flowers in short racemes of 2–5 flowers at the axils of the small branches, one pistil; calyx is a tight tube clasping the ovary with erect, inward-inclined tips, brown and reed-like on the outside. The flowers are covered with brownish scaly hairs. The pollinate greenish flowers appear before the leaves. Fruits, oval drupes, 3–11 mm long, 3–5(9) mm in diameter, turn yellow to orange when mature and persist through winter. Seeds, ovate-oblong, 3–7 mm long, 3–5 mm in diameter, dark brown to black, shiny (*4*, *8*, *9*, *20*, *22*, *27–32*).

Plant material of interest: ripe fresh berries

General appearance

The fruit is an oval, ovoid or subglobose drupe, with or without peduncle. The fruit contains an embryo encased in a seed coat that is surrounded by a thin seed sac or pericarp, all of which is enclosed in the hypanthium (fleshy portion of the fruit). The shape and colour of the fruits vary. Length between 3.5 and 11 mm and diameter up to 8.8 mm. The colour varies from yellow or bright orange to reddish orange or brownish orange. The content of carotenoids is higher in reddish-orange fruits. The fruits are easily crushed. The seed is oblong, smooth, shiny, with a longitudinal furrow, colour ranges from light or dark brown to nearly black. The average weight of 100 seeds is 1.6–2.1 g, and that of 100 berries is 57–96 g. Harvesting by removing the pedicel from the fruit, rips the epidermis, exposes fruit flesh and results in loss of juice from the fruit (*4*, *9*, *33–35*).

Organoleptic properties

Odour: light and pleasant; taste: acid, pineapple-like (*9*, *33, 34*, *36*).

Microscopic characteristics

The hypanthium, a false fruit, consists of epicarp and mesocarp. The epicarp has polygonal or polygonal-oval cells with straight irregularly thickened walls and it is confluent with the exterior of the peduncle. The epider-

mis has corymb-like trichomes characteristic for the Elaeagnaceae. The corymb-like trichomes have a continuous multicellular disc with ray-serrate edge and a multicellular stalk. The trichome stalk consists of 6–8 radial cells, which surround one or a few (2–4) smaller cells; there are numerous solitary stalks after detaching of the broken corymb-like disc. Multicellular stalks are visible through the transparent corymbs. The mesocarp of ripened fruit is liquefied. It represents a mixture of entire cells, cytoplasm, oil droplets, chromoplasts and chaotic vascular bundles. The calyx of the fruit is slightly open. There are hairs in the calyx opening, in the seed cavity and on the tail of the seed sac. The peduncle has an epidermis with corymb-like trichomes and external thick-walled cells, cortical parenchyma with sclerenchymatic cells and some primary vascular bundles arranged in circles.

The achene, the true fruit, usually known as the "seed", consists of tegument, perisperm and endosperm. The tegument is formed by thick-walled palisade cells, perpendicularly arranged on 2–3 layers of compressed parenchyma. The perisperm consists of 3–4 layers of compressed small thin-walled cells. Endosperm is a range of cells containing aleurone. The palisade cells of the cotyledons contain oil and aleurone (*2*, *37*, *38*).

Powdered plant material

Not applicable to fresh berries.

General identity tests

Macroscopic and microscopic examinations, chemical analysis and thin-layer chromatography tests for the characteristic constituents, isorhamnetin and quercetin (*39*). Flavonoids may be rapidly determined by capillary zone electrophoresis (*40*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*41*).

Chemical

A chromatographic analytical method has been described (*42*).

Foreign organic matter

Not more than 1% fragments of stems and other parts of plant. Not more than 1% of unripe berries. Not more than 2% of fruits damaged by ver-

min. Not more than 35% of bruised fruits if the juice is not lost (*1*, *2*). Not more than 4% in dried fruits (*39*).

Total ash
Not more than 1% (*1*). Not more than 6% in dried fruits (*39*).

Acid-insoluble ash
No information available on fresh fruits. Not more than 3% in dried fruits (*39*).

Sulfated ash
No information available on fresh fruits. Not less than 25% in dried fruits (*39*).

Water-soluble extractive
No information available.

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 87% (*1*).

Pesticide residues
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*43*). For other pesticides, see the *European pharmacopoeia* (*43*) and the WHO guidelines on quality control methods for medicinal plant materials (*41*) and pesticide residues (*44*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*41*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*41*) for the analysis of radioactive isotopes.

Other purity tests
Content of mineral matter not more than 0.5%. Content of acids in the fruits not more than 3% (*1*, *2*). Chemical, sulfated ash, and water-soluble

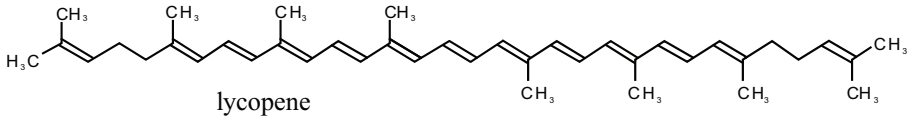
extractive tests are to be established in accordance with national requirements.

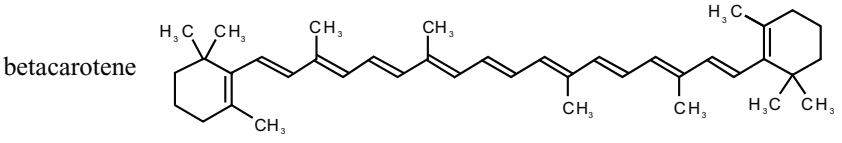
Chemical assays

Contains not less than 10 mg% of total carotenoids expressed as β-carotene (*1*, *2*). Not less than 1.5% of total flavonoids, calculated as rutin, based on the dried drug; not less than 0.10% of isorhamnetin, calculated for the dried drug (*39*).

Major chemical constituents

Vitamins and related compounds are the major biologically active constituents. Among these are carotenoids (0.04–0.1%, β- and γ-carotene together with lycopene, zeaxanthine and others), vitamin C (0.2–1.4%), vitamins of the B group (0.1–0.16%), tocopherols and tocotrienols. Other significant constituents are flavonoids (especially kaempferol, isorhamnetin, rutin and catechin, as well as quercetin tri- and tetra-glycosides). The fatty oil (in seeds commonly about 10% and up to 15–16%), consists of triglycerides rich in the two fatty acids, linoleic and α-linolenic acid; other glycerides include 1,3-decapryloyl-2-linoleyglycerol; other major fatty acids are oleic, palmitic, stearic and vaccenic acids). The fruits also contain sterols (up to 0.2% in seeds and 0.04% in soft parts, mainly β-sitosterol), tannins (hippophaenin A and B), fruit acids (chiefly malic acid), the sugar alcohols: mannitol, inositol and quebrachitol. Minerals present include selenium, zinc, calcium, iron, manganese, potassium, sodium, phosphorus, boron and copper, among others (*4*, *8*, *22*, *23*, *25*, *34*, *46–53*). The structures of the characteristic constituents are presented below.





Medicinal uses

Uses supported by clinical data

The fruits of *Hippophaë rhamnoides* are used in the treatment of cirrhosis of the liver (*54*).

Uses described in pharmacopoeias and well established documents

The fruits of *Hippophaë rhamnoides* are used to relieve cough with profuse expectoration, to promote digestion in people with prolonged gastrointestinal transit with abdominal pain, and for treatment of amenorrhoea (*39*). Fruit decoctions are used externally as a wash to treat traumatic swelling and cutaneous eruptions (*21*).

Uses described in traditional medicine

In the Islamic Republic of Iran, ethanol extracts of *Hippophaë* fruits are used internally as an astringent and anthelminthic. There are data on the use of dried fruits in patients with scurvy. *Hippophaë* fruits have been used extensively in India and Tibet for the treatment of circulatory disorders, ischaemic heart disease and hepatic injury (*55*, *56*).

Pharmacology

Experimental pharmacology

Antioxidant, radioprotective and immunomodulatory activities

The effects of an extract from fresh *H. rhamnoides* fruits and of vitamin E (positive control) against nicotine-induced oxidative stress were assessed in vitro in rat blood. Alterations in erythrocyte malondialdehyde levels, activity of some erythrocyte antioxidant enzymes, and plasma levels of vitamins E and A were determined. Groups of eight rats each were treated with: nicotine (0.5 mg/kg/day, administered intraperitoneally); nicotine + vitamin E (75 mg/kg/day, administered intragastrically); nicotine + extract (1 ml/kg/day, administered intragastrically); and a control group received no treatment. It was observed that nicotine-induced increase of malondialdehyde levels was prevented by the extract and by vitamin E. Nicotine-induced decrease in superoxide dismutase activity was prevented by the extract, but not by vitamin E. Glutathione activity was higher in the group of rats given the extract. These results suggest that extracts of *H. rhamnoides* may prevent nicotine-induced oxidative stress (*57*). The effect of an ethanol extract of *Hippophaë* fruits on radiation and chemical oxidant-mediated DNA damage was evaluated. Antioxidant activity was assessed using 2-deoxyribose degradation and 2,2-bipiridyl assays in mice. Both the in vitro and ex vivo samples were exposed to gamma ra-

diation of 1.786 Gy/sec. A dose-dependent inhibition of degradation of 2-deoxyribose was observed with a half maximal inhibitory concentration (IC_{50}) of 500 µg/ml. At concentrations of 100 and 120 µg/ml the extract inhibited radiation and DNA strand-breaks in a dose-dependent manner. At a concentration of 120 µg/ml, the extract induced chromatin compaction. A dose-dependent inhibition of degradation of 2-deoxyribose was observed with an IC_{50} of 500 µg/ml. At a concentration of 1000 µg/ml, 67% scavenging of hydroxyl radicals was observed. In ex vivo experiments, the extract prevented strand-breaks in a dose-dependent manner with a maximum effective concentration of 100 µg/ml. Post-irradiation treatment with high concentrations of the extract (150 µg/ml or more) resulted in dense compaction of chromatin (*58*, *59*). In another study, an extract of the fresh fruits was investigated for radioprotective effects in mitochondria isolated from mouse liver. Superoxide anions, reduced and oxidized succinate-cytochrome C oxidoreductase, lipid peroxidation and protein oxidation were used to measure extract-mediated radioprotection. Pretreatment of mice with the extract (30 mg/kg body weight (bw) administered intraperitoneally) before irradiation significantly inhibited radiation-induced increases in superoxide anions, glutathione levels, thiobarbituric acid reactive substances, NADH-ubiquinone oxidoreductase, NADH-cytochrome C oxidoreductase activity and mitochondrial membrane potential ($p < 0.05$). This study suggests that pre-irradiation treatment of mice with the extract protects the functional integrity of the mitochondria from radiation-induced oxidative stress (*60*). The protective effect of an ethanol extract (30 mg/kg bw) of the fruits against cobalt 60 gamma-irradiation (10 Gy) was evaluated in mice either alone or 30 minutes before irradiation. After 24 hours of irradiation, a significant reduction in splenocyte proliferation was observed (159 ± 45 counts/min/10^6 cells; in comparison with controls 607 ± 142 counts/min). Treatment with the extract before irradiation reduced the steep decrease and maintained the count at 444 ± 153 counts/min (as measured by the 3H-thymidine uptake method). At 24 hours after irradiation, the CD4/CDB lymphocyte ratio was reduced to 1.5 in comparison with the non-irradiated control (1.9), but treatment with the extract before irradiation resulted in a ratio of 2.1. These findings indicated that the immunostimulatory activity of the extract might play an important role in the manifestation of its radioprotective efficacy (*61*).

Neuroprotective action

An in vivo study examined the effect of juice from *Hippophaë* fruits on lead-induced memory impairment and neuronal damage in the brains of

mice. Mice were administered an aqueous solution of lead acetate (10 mg/kg bw per day) by intraperitoneal injection for 20 days. The juice (20% and 40%) prevented lead-induced decreases in the step-through latency test. In the water maze test, the swimming time was lengthened in mice treated with lead acetate, but was decreased in mice which received juice. The increase in malondialdehyde levels in lead-treated mice was reduced in a dose-dependent manner by the juice at concentrations of both 20% and 40%. The significantly increased activities of acetylcholinesterase and monoamine oxidase in the lead-treated group were decreased by juice at a concentration of 40%. The significantly decreased levels of norepinephrine, serotonin and 5-hydroxyindole acetic acid in the lead-treated mice were normalized by the juice at a concentration of 40% (*62*).

Antibacterial activity

Ethanol and aqueous extracts of *H. rhamnoides* fruits were screened for anti-*Helicobacter pylori* activity in vitro. The final concentrations of extracts in the medium were 200, 100, 60, 40, 20, 10 and 5 µg/ml. By using the agar dilution method, significant anti-*H. pylori* activity was detected at a minimum inhibitory concentration of approximately 60 µg/ml (*63*).

Antitumour activity

An experimental in vivo model of liver, lung and kidney carcinomas was developed by feeding Wistar rats with aminopyrine plus sodium nitrite. The control group received aminopyrine plus sodium nitrite (2 g/kg each), and the other two groups were given aminopyrine plus sodium nitrite with the addition of either ascorbic acid or the juice of *H. rhamnoides*. After 38 weeks, microscopic examination of the livers of the rats in the group that had received the juice showed fewer foci of carcinogenesis than the other groups. In addition, the average life-span was significantly longer (270 days) than that of the animals that received ascorbic acid (195 days, $p < 0.01$). The results suggest that the juice could block the in vivo synthesis of nitroso compounds in rats more effectively than ascorbic acid (*64*).

Antimutagenic effects

A study was performed to investigate the effect of juice from *Hippophaë* fruits against the genotoxic action of cisplatin in male Swiss albino mice. Both positive and negative control groups were included in the study. Freshly prepared juice (0.3 ml) was given to mice by gavage for 5 or 10 days. Three hours after the last gavage, mice received cisplatin at doses of either 1.2 or 2.4 mg/kg bw, administered intraperitoneally. The frequency of micronuclei was studied in bone marrow polychromatic eryth-

rocytes 24 hours after the injection of cisplatin. The abnormality of sperm heads was studied by microscopy. Administration of the juice decreased the number of micronuclei in bone marrow cells induced by a dose of 1.2 mg/kg of cisplatin by 36.5% and 47.9% after being given juice for 5 and 10 days, respectively (the difference between the two periods was not significant, $p > 0.05$), and by 19% (a statistically insignificant reduction, $p > 0.05$) when the dose of cisplatin was 2.4 mg/kg. The juice of Fructus Hippophaës recens thus significantly decreased the genotoxic effect of cisplatin (1.2 mg/kg) on somatic (bone marrow) and germ (sperm) cells but the decrease was not significant when the dose of cisplatin was 2.4 mg/kg. The juice similarly protected sperm heads from damage at the lower dose of cisplatin, but there was no significant protection at the higher dose (*65*).

Toxicology

The median lethal dose (LD_{50}) of a 50% ethanol-aqueous extract of the fruits has been reported as greater than 1000 mg/kg (administered by intraperitoneal injection) in mice (*66*).

Clinical pharmacology

Liver cirrhosis

The effect of an ethanol extract of *Hippophaë* fruits on the liver was assessed in a randomized clinical trial with positive controls in 50 patients with cirrhosis of the liver, which had resulted from hepatitis B or alcoholism (grades A and B according to the Child-Pugh Classification of Severity of Liver Disease). The patients were divided into two groups. Patients in the first group ($n = 30$) received 15 g of the extract by the oral route, three times a day for 6 months. Subjects in the second group ($n = 20$) took one tablet of vitamin B complex, three times a day for 6 months. The serum levels of tumour necrosis factor (TNFα), interleukin-6, serum albumin, type IV collagen, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured before and after the treatment in both groups. These substances have many biological functions, such as promoting cell proliferation and differentiation, and participation in the process of immunological reaction and inflammation. Before treatment, the peripheral blood level of the above-listed factors was significantly higher in the subjects with liver cirrhosis. After a course of treatment with the extract of *Hippophaë* fruits, the rates of normalization were 80% for ALT and AST, compared to 56% following treatment with vitamin B. The serum levels of collagen type IV, TNFα, and interleukin-6, were significantly lower in the group treated with the extract of *Hippophaë* fruit than in the group that received vitamin B ($p < 0.05$). The

results showed that the extract of *Hippophaë* fruits could reduce the serum level of factors producing liver fibrosis (*54*).

Adverse reactions
No information was found.

Contraindications
If signs of hypersensitivity reactions appear (rash, pruritus, urticaria, swelling of mouth and skin), *Hippophaë* fruits must not be used again.

Precautions
If symptoms worsen or persist for longer than 1 week or in any case of unclear symptoms, such as night sweats, increased body temperature or loss of weight, a physician should be consulted.

Drug interactions
No information was found.

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
No information was found.

Nursing mothers
No information was found.

Paediatric use
No information was found.

Dosage forms
Fresh fruits and derived infusion, tincture, oil, fresh juice and syrup (*13*, *28*, *67*).

Posology
(Unless otherwise indicated)

For internal use. Infusion: 40–50 g of the fresh fruit per litre of water, 2–3 cups per day (*68*). Tincture (1:5): 30–50 drops 1–3 times per day (*68*). Dosage of oil of *Hippophaë* fruit for internal use: one teaspoon 2–3 times daily, 30–40 minutes before meals (69, *70*).

For external use. 5–10 ml of oil per tampon, used for wetting of tampons (*71*).

References

1. *Technical standard of USSR*, 1989 (TU 64-4-87-89).
2. *The temporary monograph of Russian Federation pharmacopoeia*. Moscow, 2003 (VFS 42-0616).
3. *Northern Ontario plant database* (http://www.northernontarioflora.ca/).
4. *Herb CD4: herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific Publishers, 2001.
5. Schultze-Motel J, Mansfeld R, eds. *Verzeichnis landwirtschaftlicher und gärtnerischer Kulturpflanzen, 2. Aufl.* Berlin, Springer-Verlag, 1986.
6. *Elaeagnus rhamnoides. Plants for a future – Database search* (http://ibiblio.org/pfaf/cgi-bin/arr_html? Elaeagnus+rhamnoides&CAN=LATIND).
7. Turova AD, Sapohzhnikova FN. *Medicinal plants of the USSR and their use*. Moscow, Meditsina, 1984, 4:3–4.
8. Chevallier A. *Encyclopaedia of herbal medicine.* London, Dorling Kindersley, 2000.
9. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
10. Nadkarni AK. *Dr. Nadkarni's Indian Materia Medica*. Popular Prakashan, India, 2005.
11. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
12. Kirtikar KR, Basu BD. *Indian medicinal plants.* In 4 vols. Delhi, M/S Bishen Singh Mahendra Pal Singh, 1918.
13. Grigorescu E et al. *Index fitoterapeutic.* Bucharest, Iasi, 2001.
14. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005.
15. Bedevian AK. *Illustrated polyglottic dictionary of plant names*. Cairo, Medbouly Library, 1994.
16. Parsa A. *Flore de L'iran*. Vol. VIII. Tehran, University of Tehran, 1960.
17. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
18. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
19. Lu R. Sea buckthorn – a multipurpose plant species for fragile mountains. Katmandu, International Centre for Integrated Mountain Development, 1992:62 (ICIMOD, occasional paper no. 20).

20. Bunney S, ed. *The illustrated encyclopedia of herbs: their medicinal and culinary uses.* Prague, Chancellor Press, 1993.
21. Chevallier A. *The encyclopaedia of medicinal plants*. London, Dorling Kindersley, 1996.
22. Yakovlev GP, Blinova KF, eds. *Rastenija dlja nas*. St. Petersburg, Utchebnaja kniga, 1996.
23. Fleming T, ed. *Physicians' desk reference (PDR) for herbal medicines*. Montvale, Medical Economics Company, 2000.
24. Prokkala S. Sea buckthorn research in North Ostrobothnia in Finland. *Cost action 836. Meeting WG 6 – cane and bush fruits.* Graz, Austria, Institute of Food Chemistry and Technology, 2001:19.
25. Li TSC. *Sea buckthorn: new crop opportunity*. 1997 (http://www.hort.purdue.edu/newcrop/proceedings1999/v4-335.html).
26. Gupta A et al. A preclinical study of the effects of seabuckthorn (*Hippophaë rhamnoides* L.) leaf extract on cutaneous wound healing in albino rats. *International Journal of Lower Extremity Wounds*, 2005, 4:88–92.
27. Zadorozhnyi AM et al. *Spravotchnik po lekarstvennim rastenijam*. Moscow, Lesnaja promyshlennost', 1988.
28. Muravjova DA. *Farmakognozija*. Moscow, Meditsina, 1991.
29. Komarov VL, Shishkin BK. *Flora* SSSR. *Vol. 15.* Pod red. Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1949.
30. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR. Izd.* Moscow, Mysli, 1976.
31. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR. 3-ie izd.* Kishinev, Shtiintsa, 1986.
32. Shishkin BK. *Botaniceskii atlas* [*Botanical atlas*], pod red. Moscow-Leningrad, Izdatel'stvo sel'skokhoziaistvennoi literatury, jurnalov i plakatov, 1963 [in Russian].
33. Pantelejeva EI, Zoubarev LA. Breeding of high yielding cultivars in Russia. *Proceedings of International Workshop on Seabuckthorn*. India, 2001:83–88.
34. Yakovlev GP, Blinova KF, eds. *Lekarstvennoje rastitel'noje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
35. Shapiro DK et al. *Rastitel'nye resursy. Vol. 14.* Leningrad, Nauka, 1978.
36. Novruzov EN, Shamsizade LA, Mamedov SS. Morphological and biochemical variations in seabuckthorn (Hippophaë rhamnoides), growing in Azerbaijan. *Proceedings of International Workshop on Seabuckthorn*. India, 2001:72–77.
37. Harrison JE, Beveridge T. Fruit structure of Hippophaë rhamnoides cv. Indian Summer (sea buckthorn). *Canadian Journal of Botany*, 2002, 80:399–409.
38. Toma C, Rugina R. *Anatomia plantelor medicinale. Atlas*. Bucharest, Editura Academiei Române, 1998.
39. *Pharmacopoeia of the People's Republic of China.* Beijing, Pharmacopoeia Commission of the Ministry of Public Health, 2005.

40. Yue M-E, Jiang T-F, Shi Y-P. Fast determination of flavonoids in *Hippophaë rhamnoides* and its medicinal preparations by capillary zone electrophoresis using dimethyl-b-cyclodextrin as modifier. *Talanta*, 2004, 62:695–699.
41. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
42. Guliyev VB, Gul M, Yildirim A. *Hippophaë rhamnoides* L.: Chromatographic methods to determine chemical composition, use in traditional medicine and pharmacological effect. *Journal of Chromatography* B, 2004, 812:291–307.
43. *European Pharmacopoeia*, 5th ed. Strasbourg, Council of Europe, 2005.
44. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
45. Alam Z. Chemical and nutritional constituents of sea buckthorn juice. *Pakistan Journal of Nutrition*, 2004, 3:99–106.
46. Dharmananda S. *Sea buckthorn* (http://www.itmonline.org/arts/seabuckthorn.htm).
47. Zu Y et al. Simultaneous determination of catechin, rutin, quercetin, kaempferol and isorhamnetin in the extract of sea buckthorn (*Hippophhae rhamnoides*) leaves by PR-HPLC with DAD. *Journal of Pharmaceutical and Biomedical Analysis*, 2006, 41:714–719.
48. Swaroop A et al. Isolation and characterization of 1,3-dicapryloyl-2-linoleoylglycerol: A novel triglyceride from berries of *Hippophaë rhamnoides*. *Chemical and Pharmaceutical Bulletin,* 2005, 53:1021–1024.
49. Sabir SM et al. Elemental and nutritional analysis of sea buckthorn (*Hippophaë rhamnoides* ssp. *turcestanica*) berries of Pakistani origin. *Journal of Medicinal Food*, 2005, 8:518–522.
50. Rastogi RP, Mehrotra BN. *A compendium of Indian medicinal plants*. *Vol. 4*. Publications & Information Directorate, 1995.
51. Yang B, Kallio H. Composition and physiological effects of sea buckthorn (*Hippophaë*) lipids. *Trends in Food Science & Technology*, 2002, 13:160–167.
52. Yoshida T et al. Tannins from *Hippophaë rhamnoides*. *Phytochemistry*, 1991, 30:663–666.
53. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Rutaceae-Elaeagnaceae. Vol. 4.* Leningrad, Nauka, 1988.
54. Gao Z-L et al. Effect of sea buckthorn on liver fibrosis. A clinical study. *World Journal of Gastroenterology*, 2003, 9:1615–1617.
55. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
56. Khalmatov KH et al. *Osnovnye lekarstvennye rastenija Srednej Azii* [The main medicinal plants of Middle Asia]. Tashkent, Meditzyna, 1984.
57. Halis S et al. Beneficial effects of *Hippophaë rhamnoides* L. on nicotine induced oxidative stress in rat blood compared with vitamin E. *Biological & Pharmaceutical Bulletin*, 2002, 25:1133–1136.

58. Goel HC et al. Radioprotection by a herbal preparation of *Hippophaë rhamnoides*, RH-3, against whole body lethal irradiation in mice. *Phytomedicine*, 2002, 9:15–21.
59. Kumar IP, Namita S, Goel HC. Modulation of chromatin organization by RH-3, a preparation of *Hippophaë rhamnoides*, a possible role in radioprotection. *Molecular and Cellular Biochemistry*, 2002, 238:1–9.
60. Goel HC et al. Protection of mitochondrial system by *Hippophaë rhamnoides* l. Against radiation-induced oxidative damage in mice. *Journal of Pharmacy and Pharmacology*, 2005, 57:135–143.
61. Prakash H et al. Modification of gamma radiation induced response of peritoneal macrophages and splenocytes by *Hippophaë rhamnoides* (RH-3) in mice. *Journal of Pharmacy and Pharmacology*, 2005, 57:1065–1072.
62. Xu Y et al. Protective effects of *Hippophaë rhamnoides* L. juice on lead-induced neurotoxicity in mice. *Biological & Pharmaceutical Bulletin*, 2005, 28:490–494.
63. Yang L et al. In vitro anti-*Helicobacter pylori* action of 30 Chinese herbal medicines used to treat ulcer diseases. *Journal of Ethnopharmacology*, 2005, 98:329–333.
64. Li Yong, Liu Huang. Blocking effect of sea buckthorn juice on the formation of N-nitrosodimethylamine (NDMA) in vivo in rat. *Yingyang Xuebao*, 1989, 11:47–53.
65. Nersesyan A, Muradyan R. Sea buckthorn juice protects mice against genotoxic action of cisplatin. *Experimental Oncology*, 2004, 26:153–155.
66. Abraham Z et al. Screening of Indian plants for biological activity. Part XII. *Indian Journal of Experimental Biology*, 1986, 24:48–68.
67. Chauhan AS et al. Seabuckthorn (*Hippophaë rhamnoides* Lin.) berries: harnessing its potential for processing. *Journal of Food Sciences and Technology*, 2003, 40, 4:349–356.
68. Bézanger-Beaunesque L et al. *Plantes Médicinales des Regions Tempérèès*. Paris, Maloine, 1980.
69. Grodzinskii AM, ed. *Lekarski roslini. Entsiklopedichnyi dovidnik.* Kiiv, Redaktsija Ukrain'skoi entsiklopedii, 1991.
70. Lager AA. *Fitoterapija*. Krasnojarsk, Izdatel'stvo krasnojarskogo universiteta, 1988.
71. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.

Herba Hyperici*

Definition

Herba Hyperici consists of the dried flowering tops or aerial parts of *Hypericum perforatum* L. (Clusiaceae) (*1–3*).

Synonyms

Hypericum officinarum Crantz, *Hypericum officinale* Gater ex. Steud., *Hypericum vulgare* Lam. (*4*). Clusiaceae is also referred to as Guttiferae or Hypericaceae.

Selected vernacular names

Balsana, bassan, bossant, common St John's Wort, corazoncillo, dendlu, devil's scourge, echtes Johanniskraut, Eisenblut, erba di San Giovanni, flor de sao joao, fuga daemonum, hardhay, Hartheu, herbe à mille trous, herbe de millepertuis, Herrgottsblut, Hexenkraut, hierba de San Juan, hiperico, hipericon, houfarighoun, iperico, Jageteufel, Johannisblut, Johanniskraut, John's wort, Jottannesort, klamath weed, Konradskraut, Liebeskraut, Lord God's wonder plant, Mannskraft, millepertuis, pelicao, perforata, perforate St John's wort, pinillo de oro, quian-ceng lou, St Jan's kraut, St John's Wort, seiyouotogiri, sint janskruid, tenturotou, Teufelsflucht, Tüpfelhartheu, witches's herb, zwieroboij (*2*, *4–7*).

Geographical distribution

Indigenous to northern Africa, South Africa, South America, Asia, Australia, Europe and New Zealand, and is naturalized in the United States of America (*2*, *7*, *8*). The plant material is harvested at flowering time (*1*).

Description

A herbaceous, aromatic perennial plant, up to 1 m high; glabrous throughout, green or sometimes glaucous. Stems rounded, 2-winged, erect and branched at top. Leaves oval, linear-oblong, broadly elliptic, subcordate,

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

flat or more or less revolute-marginated with pellucid glands and sometimes a number of brown-black glandular dots. Flowers numerous, forming a broadly paniculate, compound cymose inflorescence. Petals oblong to oblong-elliptic, inequilateral with numerous glandular dots. Seed 1 mm long, cylindrical, brown, minutely pitted longitudinally (*2*, *8*, *9*).

Plant material of interest: dried flowering tops or aerial parts

General appearance

Stem glabrous greenish-yellow to brownish-yellow branching, 2-winged, cylindrical with 2 equidistant longitudinal bands. Leaves glabrous, generally sessile, opposite, greenish-grey, oval, 8–35 mm long, with entire margins; laminal margin often more or less revolute-marginated. Brown-black glandular dots sometimes present along the edges; numerous pellucid glands on the entire surface. Flowers, 2 cm in diameter, regular, forming a broadly paniculate, compound cymose inflorescence at top of stem, composed of: 5 green, lanceolate sepals, containing punctiform, black glandular dots on the edges; 5 golden-yellow petals, with numerous glandular dots along margins; and 3 staminal blades, each divided into multiple golden-yellow stamens. Anthers with single, terminal, dark pigment dot. Ovary elongated and conical, parietal placentation, carries 3 styles. Fruits trilocular capsules containing numerous brown, triangular seeds (*1–3*, *9*).

Organoleptic properties

Odour: weak, aromatic, balsamic; taste: bitter, acrid (*9–11*).

Microscopic characteristics

Transverse section of the stem circular and presents 2 lateral edges corresponding to the 2 longitudinal bands. From the exterior inwards are seen: epidermal layer formed of large polygonal cells; continuous collenchymal layer, slightly more developed at the 2 lateral edges; a cortical parenchyma containing crystals of calcium oxalate in the shape of a sea urchin; a ring of continuous phloem, distinct from the xylem, which consists of large vessels and a lignified parenchyma with a visible cambium; and a lacunose medullary parenchyma. Secretory pockets, almost invisible, rarely present in the endoderm. Upper surface of leaf section shows polygonal cells with sinuous, slightly beaded, anticlinal walls; cells of lower surface smaller, anticlinal walls more wavy with frequent paracytic, sometimes anomocytic, stomata; smooth cuticle, thicker on upper surface; straight-walled, elongated epidermal cells of veins occasionally

beaded. Dorsoventral surface of leaf consists of a single palisade layer and large oil glands. Midrib shows single, collateral bundle with small area of lignified xylem. Microscopic characteristics of the sepal resemble those of the leaf. Petal narrow, elongated, thin-walled, epidermal cells with straight anticlinal walls on outer surface and wavy on inner surface. Stamen lignified fibrous layer of anther wall; elongated, thin-walled cells of filament with striated cuticle. Pollen grains spherical or elliptical, 20–28 µm in diameter, with 3 germinal pores and smooth exine. Ovary small polygonal cells with underlying oil glands. Seed testa brown, thick-walled hexagonal cells (*2*, *3*, *9*).

Powdered plant material

Yellowish-green or brownish-green. Leaf fragments abundant, most containing large characteristic hypericin oil glands with brown to red contents. Fragments of leaf epidermis, the adaxial side with thick-walled punctate, slightly sinuate cells, and abaxial side with sinuate cells and paracytic stomata; mesophyll fragments with large secretory pockets which are spherical, bright, containing strongly refractive oil droplets; fragments of palisade parenchyma; stem fragments with reticulate spiral vessels, areolate punctation, long fibres with thick walls, ligneous parenchyma, and small number of thick-walled, characteristically punctate medullary cells; fragments of petals made of elongated rectangular cells with irregular nodulous thickenings, containing numerous yellow droplets and large, round to oval secretory pockets; fragments of anthers; pollen grains 20–28 µm in diameter, smooth spherical or elliptical with 3 germinal pores; clusters of calcium oxalate crystals (*1*, *2*).

General identity tests

Macroscopic and microscopic examinations and thin-layer chromatography for the presence of characteristic compounds (hypericin, pseudohypericin, chlorogenic acid, hyperoside) (*1*, *9–11*). Additionally, a liquid chromatography–mass spectrometry method is available (*12*). The presence of hyperforin and rutin in Herba Hyperici is used to differentiate *Hypericum perforatum* from other *Hypericum* species (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter
Not more than 3% stems with a diameter greater than 5 mm (*1*) and not more than 2% other foreign matter (*1*, *3*).

Total ash
Not more than 7% (*1*).

Acid-insoluble ash
Not more than 2.5% (*9*).

Sulfated ash
Not more than 2.5% (*9*).

Water-soluble extractive
Not less than 12% (*9*).

Loss on drying
Not more than 10% (*1*, *3*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

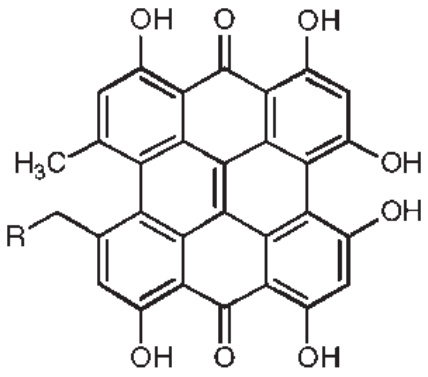
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests
Chemical and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.08% hypericins calculated as hypericin, as determined by spectrophotometry (*1*). Quantitation can also be obtained by high-performance liquid chromatography (*2*, *16*).

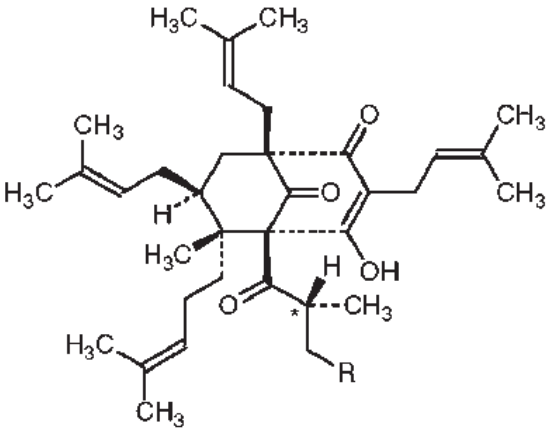
Major chemical constituents

The major characteristic constituents include 0.05–0.30% naphthodianthrones (hypericin, pseudohypericin, hyperforin, adhyperforin); 2–4% flavonoids (hyperoside, quercitrin, isoquercitrin, rutin); and 7–15% catechin tannins (*2*, *4*, *7*, *17*). The structures of the representative constituents are presented below.



hypericin R = H

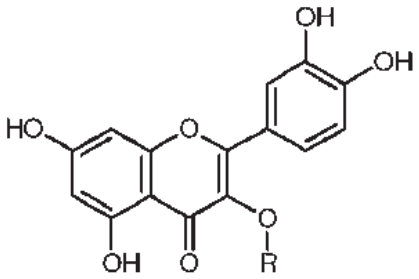
pseudohypericin R = OH



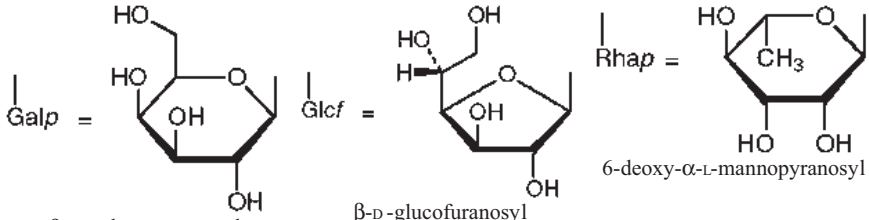
and epimer at C*

hyperforin R = H

adhyperforin R = CH_3



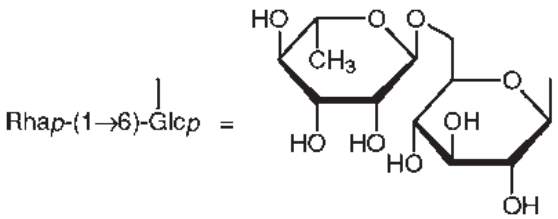
quercitrin	R = Rha*p*
hyperoside	R = Gal*p*
isoquercitrin	R = Glc*f*
rutin	R =Rha*p*-(1→6) -Glc*p*



β-D-galactopyranosyl

β-D-glucofuranosyl

6-deoxy-α-L-mannopyranosyl



O-6-deoxy-α-L-mannopyranosyl-(1→6)-β-D glucopyranosyl

Medicinal uses

Uses supported by clinical data

Symptomatic treatment of mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in the *International statistical classification of diseases and related health problems, Tenth revision (ICD-10) (18)*) (*19–31*).

Uses reported in pharmacopoeias and in traditional systems of medicine

Externally for the treatment of minor cuts, burns and skin ulcers (*8*, *32*). Topically for viral infections (*33*).

Uses described in folk medicine, not supported by experimental or clinical data

As an antiphlogistic agent in the treatment of inflammation of the bronchi and urogenital tract; treatment of biliary disorders, bladder irritation, the common cold, diabetes mellitus, dyspepsia, haemorrhoids, neuralgia, migraine headaches, sciatica and ulcers (*5*, *8*). Also used as a diuretic, an emmenagogue and an antimalarial agent (*5*, *8*).

Pharmacology

Experimental pharmacology

Antidepressant activity

Behavioural studies, performed primarily in rodents, have demonstrated the antidepressant activity of Herba Hyperici by measuring the exploratory and locomotor activities of animals in an unknown environment (*34*, *35*). Intragastric administration of a 95% ethanol extract of the herb to male gerbils (2 mg/kg body weight) suppressed clonidine-induced depression. Intragastric administration of the extract to male mice (5 mg/kg body weight) enhanced exploratory activity in a foreign environment and significantly prolonged narcotic-induced sleeping time in a dose-dependent manner; the treated mice also exhibited reserpine antagonism. Similar to standard antidepressant drugs, the extract (6 mg/kg body weight) increased the activity of mice in the waterwheel test following a single dose; prolonged administration (6 mg/kg body weight, daily for 3 weeks) decreased aggressiveness in socially isolated male mice (*35*). Intraperitoneal administration of a 50% ethanol extract of the herb to mice (250 mg/kg body weight) reduced the tail flick response to radiant heat, and significantly decreased swimming time in the forced swimming test ($P < 0.05$) and walking time on a rotating rod ($P < 0.005$), as well as exploratory activity ($P < 0.05$) (*36*). Significant, dose-dependent, antidepressant activities were observed in the behavioural despair test and the learned helplessness paradigm in rats treated intragastrically with a carbon dioxide extract of the crude drug containing 38.8% hyperforin (30 mg/kg body weight) or an ethanol extract containing 4.5% hyperforin (300 mg/kg body weight) ($P < 0.001$). The results were comparable to those obtained following intraperitoneal administration of imipramine (10 mg/kg body weight) (*37*). Intragastric adminis-

tration of an ethanol extract containing 4.5% hyperforin (50, 150 and 300 mg/kg body weight, daily for 3 days) or a carbon dioxide extract devoid of hypericin but containing 38.8% hyperforin (5, 15 and 30 mg/kg body weight, daily for 3 days) had similar antidepressant activity in rodents (rats and mice) (*38*, *39*). In the same dosage range, the ethanol extract potentiated dopaminergic behavioural responses, whereas these effects were either absent or less pronounced in rodents treated with the carbon dioxide extract. In contrast, serotoninergic effects of the carbon dioxide extract were more pronounced than those of the ethanol extract (*38*). Intragastric administration of a methanol extract containing both hypericin and pseudohypericin (500 mg/kg body weight) to mice produced a dose-dependent increase in ketamine-induced sleeping time and also increased body temperature. The extract also decreased immobility time in the tail suspension test and forced swimming tests, which are both regarded as indicative of antidepressant activity (*40*). Intragastric administration of a 50% ethanol extract of the herb prolonged pentobarbital-induced sleeping time (13.25 mg/kg body weight) and depressed the central nervous system in male mice (25.50 mg/kg body weight). The observed effects were similar to those seen in mice treated with diazepam (2 mg/kg body weight) (*41*). Measurement of some metabolites of biological amines in the urine of various animal models has established a correlation between the excretion in the urine of 3-methoxy-4-hydroxyphenylglycol, the main metabolite of noradrenaline, with the start of the therapeutic antidepressant activity (*42*).

A hydroalcoholic extract of the herb inhibited serotonin (5-hydroxytryptamine, 5-HT) receptor expression in mouse brain synaptosome preparations in vitro (50 µmol/l), and similar effects were observed during *ex vivo* experiments (*43*). In other studies, hydroalcoholic extracts of the herb inhibited serotonin reuptake (IC_{50} 6.2–25.0 µg/ml) (*44*, *45*), and inhibited both γ-aminobutyric acid (GABA) reuptake (IC_{50} 1 µg/ml) and GABA type A receptor binding (IC_{50} 3 µg/ml) in vitro (*46*).

A hydroalcoholic extract of the fresh flowers and buds of *H. perforatum* (containing 0.1% hypericin) was subjected to a series of assays involving 39 receptor types and two enzymes. Receptor assays exhibiting at least 50% radioligand displacement or 50% inhibition of monamine oxidase (MAO) were considered to be active. The extract demonstrated specific affinity for the GABA (types A and B), serotonin, benzodiazepine and inositol triphosphate receptors, nonspecific affinity for adenosine receptors and inhibited MAO types A and B. Purified hypericin lacked any significant MAO (type A or B)-inhibitory activity at concentrations up to 10 µmol/l, and had affinity only for *N*-methyl-D-aspartate (NMDA) receptors in rat forebrain membranes (*47*).

An ethanol extract of the herb inhibited radioligand binding to the NMDA, GABA type A and GABA type B receptors (IC_{50} 7.025, 3.240 and 3.310 µg/ml, respectively). The extract also inhibited synaptosomal GABA and L-glutamate uptake in vitro (IC_{50} 1.11 and 21.25 µg/ml, respectively) (*48*).

A methanol or carbon dioxide extract of the herb, and pure hyperforin significantly inhibited synaptosomal uptake of serotonin, noradrenaline, dopamine, L-glutamate and GABA in vitro (*49*). The carbon dioxide extract (containing 38.8% hyperforin) was more active than the methanol extract (containing 4.5% hyperforin), due to the higher hyperforin concentration. Inhibition was most pronounced with purified hyperforin, showing the following order of affinity: noradrenaline ≥ dopamine > GABA ≥ serotonin >> glutamate (IC_{50} 0.043–0.445 µg/ml) (*49*, *50*). Neither hyperforin nor the carbon dioxide extract inhibited the activity of MAO type A or B at concentrations up to 50 µg/ml (*49*).

A methanol extract of dried *H. perforatum* flowers inhibited radiolabelled-flumazenil binding to the benzodiazepine sites of the GABA receptor in rat brain preparations in vitro (IC_{50} 6.83 µg/ml) (*51*). The number of serotonergic 5-HT_1 A and 5-HT_2 A receptors significantly increased in the brains of rats treated with an ethanol extract of the herb (2.7 g/kg body weight) daily for 26 weeks, whereas the affinity of both serotonergic receptors remained unaltered. These data suggest that prolonged administration of the extract induced upregulation of the 5-HT_1 A and 5-HT_2 A receptors (*52*). The affinity of hypericin for 30 types of receptor and reuptake sites was determined in vitro. At 1 µmol/l, hypericin inhibited less than 40% specific radioligand binding at all sites tested, except binding at the acetylcholine and sigma receptors (*53*).

The mechanism of the antidepressant effect of Herba Hyperici is not well understood. Early studies focused on the inhibition of MAO and catechol-*O*-methyltransferase (COMT), the two enzymes responsible for the catabolism of biological amines, such as serotonin. Initial investigations analysed the in vitro inhibition of MAO using a series of xanthones isolated from extracts of the herb (*54*, *55*). In later studies, hypericin was reported to inhibit MAO type A (IC_{50} 6.8×10^{-5} mol/l) and type B (IC_{50} 4.2×10^{-5} mol/l) in rat brain mitochondria in vitro (*56*). However, analysis of the hypericin fraction used in these experiments revealed that at least 20% of the extract was composed of other constituents, including some flavonoid derivatives (*8*). Xanthone-containing fractions, free of hypericin and tannins, of a hydroalcoholic extract of *H. perforatum* showed significant inhibition in vitro of MAO type A (which is specific for serotonin) (*57*). In other investigations, only the flavone aglycone,

quercitrin, and the xanthone derivative, norethyriol, showed significant inhibition of MAO type A (*57–59*). Hypericin was excluded as the active constituent, and the flavonols and 1,3,6,7-tetrahydroxyxanthone were reported to be the active constituents of a crude extract of the herb (*57–59*). Molecular modelling studies of the constituents of the herb also indicated that the flavonoids may be the most likely candidates for inhibitors of MAO, as their structures are similar to those of known MAO type A inhibitors, toloxotone and brofaromine (*60*).

The MAO-inhibiting activity of six fractions of a hydroalcoholic extract of the herb was determined in vitro and *ex vivo*. In vitro inhibition of MAO type A in rat brain homogenates could only be shown at a concentration of 1–10 mmol/l of a crude extract or a flavonoid-rich fraction. In *ex vivo* studies using albino rats, neither the crude extract nor the xanthone-containing fractions inhibited MAO type A or MAO type B after intraperitoneal administration of 300 mg/kg body weight of the extract or 1–10 nmol/l of the fractions. In addition, purified hypericin did not inhibit MAO type A either in vitro or *ex vivo* (*61*).

The in vitro effects of hypericin, an ethanol extract, and fractions of the extract were tested for inhibition of MAO and COMT obtained from pig liver. Inhibition of MAO was seen with hypericin (1 mmol/l),[1] ethanol extract (0.1 mmol/l),[1] and a fraction containing hypericins and flavonols (0.01 mmol/l).[1] Weak inhibition of COMT was observed with hypericin and the ethanol extract (both at a concentration of 1 mmol/l),[1] whereas two fractions, containing flavonols and xanthones, inhibited COMT to a greater extent at 0.1 mmol/l [1] (*62*). However, the inhibitory concentrations observed during this study appear to be too high to be of any clinical significance.

Other possible mechanisms of the antidepressant effect of Herba Hyperici include its ability to modulate the production of mediators of inflammation such as cytokines, particularly interleukins. Strong suppression of interleukin-6 (IL-6) release was observed in blood samples from depressed patients treated with *H. perforatum* extract (*63*). IL-6 is involved in the modulation of the hypothalamic-pituitary-adrenal (HPA) axis within the nervous/immune system. Elevated IL-6 levels activate the HPA axis, thus increasing levels of adrenal hormones that play a role in depression.

[1] Molar concentrations were based on a mean molar mass of 500 (62).

Effect on smooth muscle contraction

A 95% ethanol extract or tincture of the herb (200 µg/ml) inhibited barium- and histamine-induced smooth muscle contractions of guinea-pig ileum in vitro (*64*), and contractions of cat and mouse intestine (*65*). An ethyl acetate extract of the herb (0.1 mg/ml) inhibited potassium chloride- and histamine-induced contractions in pig coronary artery in vitro (*66*).

Antibacterial and antiviral activity

A methanol extract of Herba Hyperici inhibited the growth in vitro of *Escherichia coli*, *Proteus vulgaris*, *Streptococcus mutans*, *Streptococcus sanguis*, *Staphylococcus oxford* and *Staphylococcus aureus (*MIC 0.31–1.25 mg/ml) (*67*). An acetone, hot aqueous or ethyl acetate extract of the herb was active against influenza virus A2 (Mannheim 57), herpes simplex virus 2, poliovirus II and vaccinia virus in vitro (*68*, *69*). However, a decoction or hydroalcoholic extract of *H. perforatum* dried stem was not active against herpes simplex virus 1 or 2, or HIV in vitro (100 µg/ml) (*70*). In vitro activity of hypericin has been demonstrated against Friend murine leukaemia virus, hepatitis B virus, murine cytomegalovirus, human cytomegalovirus (Davis strain), parainfluenza 3 virus, Sindbis virus, vaccinia virus, vesicular stomatitis virus and equine infectious anaemia virus (*71–77*). Hypericin and pseudohypericin also inhibited herpes simplex virus types 1 and 2, and HIV-1 in vitro (*75*, *77–83*). Hypericin inhibited the activity of HIV reverse transcriptase in vitro (IC_{50} 0.77 mmol/l) (*74*, *80*, *84*), and inhibited herpes simplex virus, Rauscher murine leukaemia and Friend murine leukaemia viruses in mice after intravenous, intraperitoneal or intragastric administration (*80–82*). Intraperitoneal administration of a 5% aqueous extract of the herb to mice resulted in viricidal activity against tick-borne encephalitis virus (*85*). Hypericin displayed marginal activity in vitro against Molony murine leukaemia virus and did not show selective activity against herpes simplex virus, influenza virus A, adenovirus or poliovirus (*82*). However, incubation of the virus with hypericin prior to infection resulted in viricidal activity against all enveloped viruses tested (IC_{50} 1.56–25 µg/ml), but not against non-enveloped viruses (*82*). The antiviral activity of hypericin appears to involve a photoactivation process that forms a singlet oxygen and inactivates both viral fusion and syncytia formation (*72*, *75*, *86*).

Protein kinase C inhibition

Numerous in vitro studies have demonstrated that hypericin is a potent inhibitor of protein kinase C (*87–92*). Hypericin treatment of glioma cell lines inhibited growth and also induced cell death due to protein kinase C

(*93*). Receptor tyrosine kinase activity of epidermal growth factor is also inhibited by hypericin and may be linked to its antiviral and antineoplastic effects (*89*, *94*). The inhibition of protein kinase C may contribute to the anti-inflammatory effects of Herba Hyperici, as hypericin also inhibited the release of arachidonic acid and leukotriene B4 (*94*).

Wound healing

External application of a 20% aqueous extract of the crude drug to the skin of guinea-pigs and rabbits accelerated healing of experimentally induced wounds (*95*, *96*). Intragastric administration of a 60% ethanol extract of the dried leaves to rats (0.1 ml/animal) accelerated healing of experimentally induced wounds by enhancing the strength and rate of wound contraction and epithelialization (*97*).

Clinical pharmacology

Antidepressant activity

Clinical trials without controls

The safety and efficacy of oral administration of Herba Hyperici has been assessed in more than 5000 patients in numerous case-reports and studies (*22*, *23*, *31*, *98*). In a drug-monitoring study involving 3250 patients, 49% were assessed as being mildly depressed, 46% as moderately depressed and 3% as severely depressed at the beginning of the trial. The patients were treated with 300 mg of a dried 80% methanol extract of the herb three times daily, and evaluated after 2 and 4 weeks of therapy. After treatment, 80% of patients had improved or were symptom-free, while 13–16% remained unchanged or were worse. Minor adverse reactions were reported in 2.4% of patients (*31*). A postmarketing trial was performed with 2404 patients with symptoms of mild to moderate depression who were treated with 2–4 capsules of an ethanol extract of the herb (equivalent to 0.6–1.8 mg total hypericin) daily for 4–6 weeks. Symptomatic improvement was evaluated as good to very good in 77% of patients and satisfactory in 15% (*99*).

The effects of an ethanol extract of the herb on the electroencephalogram (EEG) of 40 patients with depression were determined following administration of the extract (equivalent to 0.5 mg total hypericin or 1.4 g crude drug) daily for 4 weeks. An increase in theta-activity, a decrease in alpha-activity and no change in beta-activity were observed, indicating the induction of relaxation (*100*). A significant increase in nocturnal melatonin plasma concentration was observed in 13 healthy subjects treated with a hydroethanolic extract of the herb (equivalent to 0.53 mg total

hypericin) daily for 3 weeks (*101*). A significant increase in the concentration of neurotransmitters in the urine was observed 2 hours after administration of a standardized ethanol extract of the crude drug to six women with symptoms of depression (*42*).

Reviews of clinical trials

The results from over 28 controlled clinical trials involving oral administration of Herba Hyperici have been published. Twelve of the trials, involving 950 patients, were conducted using an ethanol extract of the herb, while the other 16 trials of 1170 patients used a dried 80% methanol extract (*26*). A systematic review and meta-analysis of 23 of the randomized clinical trials involving 1757 patients assessed the efficacy of the herb in the symptomatic treatment of mild to moderate depression. Twenty trials were double-blind, one was single-blind and two were open studies. Fifteen of the trials involving 1008 patients were placebo-controlled and eight studies of 749 patients were comparison trials with other antidepressant drugs. With the exception of two trials, all studies had treatment periods of 4–8 weeks. The daily dosage ranged from 0.4 to 2.7 mg hypericin in 300–1000 mg of a standardized extract of the herb. Seventeen trials used the Hamilton Rating Scale for Depression (Hamilton Depression Rating Scale), which focuses primarily on somatic symptoms, to measure effectiveness, while 12 trials used the Clinical Global Impression Scale. The latter involves observer-rated analysis of severity of illness, global improvement and efficacy. The meta-analysis concluded that the herb was significantly superior to the placebo and was as effective as standard antidepressants such as maprotiline or imipramine (75 mg three times daily). Fewer side-effects were seen in the herb-treated patients (19.8%) than in those receiving standard antidepressants (52.8%) (*21*).

A systematic, criteria-based review of 18 controlled clinical trials using either ethanol or methanol extracts of the herb as a treatment for depression was carried out. Twelve of the trials (nine placebo-controlled and three comparison trials) met the methodological inclusion criteria and were included in the review. The results of the cumulative data show that extracts of the herb were superior to the placebo for the symptomatic treatment of depression as measured by the Hamilton Depression Rating Scale. Results of the comparison studies with maprotiline (75 mg daily) and imipramine (50–75 mg daily) and other standard antidepressants suggest that extracts of the herb have a similar therapeutic profile. Some flaws in the reported studies included no intention to treat analysis, lack of control over compliance, and insufficient description of the extract or placebo used (*19*).

A review of 12 double-blind, placebo-controlled and three comparison clinical trials assessed the efficacy of the herb for the treatment of mild to moderate depression, and the methodology used to perform the studies. The review concluded that the antidepressant activity of a standardized extract of the herb (300 mg standardized to contain 0.9 mg hypericin three times daily for 4–8 weeks) was sufficiently documented. However, it also concluded that no dose-finding studies had been conducted, and that studies on inpatients with severe depression and endogenously depressed patients were lacking. In the three comparison studies, the daily dose of 75 mg maprotiline or 30 mg amitriptyline was viewed as too low. The review concluded that further trials of longer duration in comparison with higher doses of standard antidepressants are warranted (*27*).

A double-blind, randomized, multicentre study was performed to evaluate the efficacy, safety and tolerability of a daily dose of 900 mg hydroalcoholic extract of the herb or 75 mg amitriptyline. After a 1-week placebo run-in phase, 156 patients were treated with 300 mg extract or 25 mg amitriptyline, three times daily for 6 weeks. The patients were assessed before and after treatment. The Hamilton Depression Rating Scale changed from 20 to 10 in the extract-treated patients and from 21 to 6 in the amitriptyline-treated patients ($P < 0.05$). The Montgomery-Asberg Rating Scale for Depression changed from 27 to 13 in the extract-treated patients, and from 26 to 6.5 in the amitriptyline-treated patients ($P < 0.05$). Similar scores in the Clinical Global Impression Scale were observed in both groups (*29*). In a randomized, double-blind, multicentre trial the effectiveness of a standardized dried 80% methanol extract of the herb (containing 0.3% hypericin) was compared with that of imipramine in 209 patients with recurrent depressive disorder, current episode severe without psychotic symptoms (*18*). Patients were treated daily with 1800 mg extract or 150 mg imipramine for 6 weeks. Assessment of patients before and after treatment revealed the following changes. In the Hamilton Depression Rating Scale: from 25.3 to 14.4 in the extract-treated patients, and from 26.1 to 13.4 in the imipramine-treated patients ($P < 0.021$). In the von Zerssen Depression Scale: from 28.9 to 13.6 in the extract-treated patients, and from 26 to 6.5 in the imipramine-treated patients ($P < 0.05$). Results in the Clinical Global Impression Scale showed a trend in favour of imipramine. Although the efficacy of the extract was not significantly different from that of imipramine, analysis of the patient subgroups showed that it was most effective in patients with moderately severe depression (*28*).

A prospective, randomized, double-blind, placebo-controlled, multicentre study assessed the safety and efficacy of a standardized ethanol ex-

tract of the herb for the treatment of 151 patients with mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in 1CD-10 (*18*)). Patients received either one 250 mg tablet of the extract (equivalent to 1 mg hypericin) or a placebo twice daily for 6 weeks. The primary efficacy variable was the Hamilton Depression Rating Scale, and secondary variables were the risk–benefit Clinical Global Impression Scales I–III and Visual Analogue Scale (a validated, patient self-assessment test). Decreases were seen in the Hamilton Depression Rating Scale in 56% of patients treated with the extract, whereas decreases were seen in only 15% of patients who received the placebo (*24*). A randomized, double-blind, placebo-controlled, multicentre study assessed the clinical efficacy and safety of two extracts of the herb differing in their hyperforin content (0.5% or 5.0% hyperforin) in 147 patients suffering from mild to moderate depression as classified in the *Diagnostic and statistical manual of mental disorders*, 4th ed. (DSM-IV) of the American Psychiatric Association (*102*). The patients received either 900 mg of one of the extracts or a placebo daily for 42 days. The patients who received the extract containing 5% hyperforin showed the largest decrease in the Hamilton Depression Rating Scale (a reduction of 10.3; $P = 0.004$, compared to the placebo). A reduction of 8.5 following treatment with the extract containing 0.5% hyperforin and of 7.9 in the placebo-treated group was seen (*20*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers treated with a dried hydromethanolic extract of the herb (300 mg three times daily for 4 weeks) showed improved sleep quality with an increase in deep-sleep phases (*25*). A randomized, double-blind, placebo-controlled study of 54 healthy volunteers evaluated the central pharmacodynamic effects of two extracts of the herb with different hyperforin contents (0.5% or 5.0%) but identical hypericin content. Healthy volunteers received either 900 mg (300 mg three times daily) of one of the extracts or a placebo daily for 8 days. A quantitative topographic electroencephalogram (qEEG) was performed on days 1 and 8 as an indicator of drug-induced pharmacological activity. In both treatment groups, reproducible central pharmacodynamic effects were observed between 4 and 8 hours after administration, and were confirmed on day 8. The extract containing 5% hyperforin showed a marked tendency to produce greater increases in qEEG baseline power performances than the extract containing 0.5% hyperforin. Higher baseline outputs were observed on day 8 in the delta-, theta- and alpha-1 frequencies. Patients treated with the extract containing 5% hyperforin had an increase in qEEG power performance in the delta-frequency after a single dose and in the theta- and alpha-1 frequencies after 8 days of treatment, when compared with placebo treatment (*103*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers were treated with 900 mg (300 mg three times daily) of a dried hydromethanolic extract of the herb for 6 weeks, and the effects on the EEG were assessed. A reduction in alpha-activity and audiovisual latencies in evoked potentials and an increase in beta- and theta-activities were demonstrated (*104*). Another randomized, double-blind, clinical trial of 24 healthy volunteers compared the effects of a dried hydromethanolic extract of the herb with those of maprotiline on the resting EEG and audiovisual latencies in evoked potentials. After 4 weeks of treatment, an increase in theta- and beta-2 activity was observed in patients treated with 900 mg of a standardized hydroalcoholic extract (300 mg three times daily), while a decrease in theta-activity was seen in patients treated with 30 mg maprotiline (10 mg three times daily) (*105*). The extract also induced an increase of deep sleep as demonstrated by visual analysis of the sleeping phases and automatic analysis of slow-wave EEG activities. Rapid eye movement sleep was not influenced (*25*).

A randomized, single-blind study evaluated the efficacy of the herb for the treatment of seasonal affective disorders (SAD) in conjunction with light therapy. Twenty patients with SAD were treated with 900 mg (300 mg three times daily) of a hydroalcoholic extract of the herb daily for 4 weeks, combined with either bright (3000 lux) or dim light (<300 lux) conditions. Light therapy was carried out for 2 hours daily. A significant reduction of the Hamilton Depression Rating Scale in both groups, but no statistically significant difference between the two groups, was observed (*106, 107*).

Photodynamic effects

The photodynamic effects of hypericin, incorporated into a non-ionic hydrophilic ointment base, were assessed after external application to the skin of patients with herpes communis. The infected dermal surface of treated patients recovered rapidly and the effects lasted in most cases (*33*).

Pharmacokinetics

Single-dose pharmacokinetics of hypericin and pseudohypericin were determined in 12 healthy male volunteers. After a single dose of 300, 900 or 1800 µg extract (equivalent to 250, 750 or 1500 mg hypericin, respectively, and 526, 1578 or 3156 µg pseudohypericin, respectively), plasma levels of the hypericins were measured by high-performance liquid chromatography for up to 3 days. The median plasma levels were 1.5, 4.1 and 14.2 ng/ml for hypericin, and 2.7, 11.7 and 30.6 ng/ml for pseudohypericin, for the three stated doses, respectively. The median half-life of hypericin was

24.8–26.5 hours and 16.3–36.0 hours for pseudohypericin. The median lag-time of absorption was 2.0–2.6 hours for hypericin and 0.3–1.1 hours for pseudohypericin. During long-term dosing (900 mg daily), a steady state was reached after 4 days. The mean maximum plasma level during the steady state was 8.5 ng/ml for hypericin and 5.8 ng/ml for pseudohypericin (*108*).

A randomized, placebo-controlled clinical trial was performed to evaluate the pharmacokinetics and dermal photosensitivity of hypericin and pseudohypericin in 13 healthy volunteers after administration of a single dose of either a placebo or 900, 1800 or 3600 mg of the extract (equivalent to 0.00, 2.81, 5.62 and 11.25 mg total hypericin [combined hypericin and pseudohypericin], respectively). The maximum total hypericin plasma levels observed at 4 hours after administration were 0, 28, 61 and 159 ng/l, respectively. Before and 4 hours after drug intake, the subjects were exposed to increasing doses of solar-simulated irradiation on small areas of their backs. No dose-related increase in light sensitivity was observed. In the multiple-dose analysis, 50 healthy volunteers received 600 mg extract of the herb three times during 1 day only. A slight increase in solar-simulated irradiation sensitivity was observed (*109*).

In a randomized, four-way crossover study without controls involving six healthy volunteers, the pharmacokinetics of hyperforin were determined after administration of single doses of 300, 600, 900 or 1200 mg of an alcohol extract containing 5% hyperforin. The maximum plasma level of hyperforin (150 ng/ml) was reached 3.5 hours after administration of 300 mg of the extract. The hyperforin half-life and mean residence time were 9 and 12 hours, respectively. The pharmacokinetics were linear up to 600 mg of the extract. Increasing the dose to 900 or 1200 mg of extract resulted in values for maximum clearance and area under the curve lower than those expected from linear extrapolation of data from the lower doses (*110*). The pharmacokinetics of hyperforin were studied in nine healthy volunteers, as part of a double-blind, randomized, placebo-controlled study of 54 subjects. The subjects received either a single dose of 900 mg of an alcohol extract containing 5% hyperforin, or 300 mg of an alcohol extract containing 5% hyperforin three times daily for 8 days. No accumulation of hyperforin in the plasma was observed. On the basis of the area under the curve values from the multiple-dose study, the estimated steady-state plasma concentration of hyperforin was approximately 100 ng/ml (*110*).

Contraindications

Herba Hyperici is contraindicated in cases of known allergy to plants of the Clusiaceae family.

Warnings

As with other antidepressant drugs, observation of the therapeutic effects of Herba Hyperici may require 2–4 weeks of therapy. If a significant antidepressant effect is not observed after 6 weeks of treatment, a physician should be consulted.

Precautions

General

Ultraviolet treatments or prolonged exposure to direct sunlight should be avoided when Herba Hyperici is used, as photosensitization may occur in light-sensitive individuals (*32*). (See Adverse reactions.)

Drug interactions

Although the ingestion of foods containing high concentrations of tyramine such as pickled or smoked foods and cheese, and selective serotonin reuptake inhibitors such as fluoxetine are contraindicated with MAO inhibitors, in vivo data linking Herba Hyperici to MAO inhibition are lacking (*111*, *112*). The combination of Herba Hyperici with other standard antidepressant drugs, such as tricyclic antidepressants or fluoxetine, is not recommended, unless under medical supervision.

There are now numerous reports in the medical literature indicating that Herba Hyperici extracts induce hepatic enzymes that are responsible for drug metabolism and may reduce the serum levels and therapeutic efficacy of drugs (*113–117*). Coadministration of theophylline with a Herba Hyperici extract lowered the serum level of theophylline in a patient previously stabilized, requiring an increase in the theophylline dose (*113*). Coadministration of Herba Hyperici and digoxin reduced serum digoxin concentrations after 10 days of treatment (*114*). A decrease in serum cyclosporin, warfarin and phenprocoumon concentrations was seen in patients after they had additionally taken Herba Hyperici extracts (*115*). Concomitant use of Herba Hyperici in five patients previously stabilized on serotonin-reuptake inhibitors resulted in symptoms of central serotonin excess (*116*). The United States Food and Drug Administration has publicized a report concerning a significant drug interaction between Herba Hyperici and indinavir, a protease inhibitor used to treat HIV infections (*117*). Herba Hyperici substantially reduced indinavir plasma concentrations, due to induction of the cytochrome P450 metabolic pathway. As a consequence, the concomitant use of Herba Hyperici and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended and may result in suboptimal antiretroviral drug concen-

trations, leading to a loss of virucidal activity and the development of resistance (*117*).

Carcinogenesis, mutagenesis, impairment of fertility

The mutagenicity of hydroalcoholic extracts of Herba Hyperici containing 0.2–0.3% hypericin and 0.35 mg/g quercetin has been studied in various in vitro and in vivo systems (*118–121*). The in vitro studies were performed using the *Salmonella*/microsome assay, hypoxanthine guanidine phosphoribosyl transferase test (up to 4 µl/ml), unscheduled DNA synthesis test (up to 1.37 µl/ml), cell transformation test in Syrian hamster embryo cells (up to 10 µl/ml) and spot test in mice (up to 10 µl/ml). The in vivo tests included the chromosome aberration test with bone marrow cells of Chinese hamsters (10 ml/kg body weight, gastric lavage) and the micronucleus test in rodent bone marrow (2 g/kg body weight, gastric lavage). Although some positive results were observed in vitro in the *Salmonella*/microsome assay (*119*, *121*), all the in vivo tests were negative, indicating that the hydroalcoholic extract was not mutagenic in animals. In a 26-week study, intragastric administration of the hydroalcoholic extract to rats and dogs (900 and 2700 mg/kg body weight) had no effect on fertility, development of the embryo, or pre- or postnatal development (*122*).

Other precautions

No information available on precautions concerning drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Herba Hyperici should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Phototoxicity has been reported in cattle after ingestion of *H. perforatum* during grazing. However, the doses were estimated to be approximately 30–50 times higher than normal therapeutic doses (*123*). Photosensitization in light-sensitive individuals has been demonstrated in a controlled clinical trial involving metered doses of hypericin and exposure to ultraviolet A and B irradiation. Patients were treated with 600 mg of a hydroalcoholic extract of the herb (containing 0.24–0.32% total hypericin) three times daily for 15 days. A measurable increase in erythema in light-sensitive individuals was observed after ultraviolet A irradiation. The plasma concentration of hypericin and pseudohypericin in these subjects was double that seen during normal therapeutic treatment of depression (*124*). A single case of reversible erythema after exposure to ultraviolet B

has been reported in one patient who had been taking the herb for 3 years (*125*). A single case of acute neuropathy after exposure to sunlight has been reported in one patient taking the herb (*126*). Drug-monitoring studies indicate that side-effects of the herb are rare and mild, and include minor gastrointestinal irritations, allergic reactions, tiredness and restlessness. However, these studies did not last longer than 8 weeks (*21*, *24*, *31*). Clinical studies have suggested that the use of the herb does not affect general performance or the ability to drive (*127*, *128*).

Dosage forms

Dried crude drug for decoction, powdered drug or extracts in capsules, tablets, tinctures and drops (*2*, *7*, *32*). Topical preparations include the oil, infusions, compresses, gels and ointments. Store in a well-closed container, protected from light (*10*, *11*).

Posology

(Unless otherwise indicated)

Daily dosage: 2–4 g crude drug (*32*). Internal use: standardized tinctures or fluidextracts (*23*, *98*, *100*), or standardized hydroethanolic or dried hydromethanolic extracts, up to a daily dose of 900 mg extract (equivalent to 0.2–2.7 mg total hypericin) (*19*, *21*, *22*, *27*, *31*).

References

1. *European pharmacopoeia*, 3rd ed., Suppl. 2000. Strasbourg, Council of Europe, 1999.
2. *American herbal pharmacopeia and therapeutic compendium*. Santa Cruz, CA, American Herbal Pharmacopeia, 1997.
3. St John's wort. *In: The United States pharmacopeia 24: national formulary 19*. Rockville, MD, United States Pharmacopeial Convention, 2000:2509–2510.
4. Blaschek W et al., eds. *Hägers Handbuch der pharmazeutischen Praxis*. *Folgeband 2: Drogen A-K*, 5th ed. Berlin, Springer-Verlag, 1998.
5. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
6. Pignatti S. *Flora Italica*. Torino, Unione Tipografico Editrice Torinese, 1982.
7. Bisset NG. *Herbal drugs and phytopharmaceuticals.* Boca Raton, FL, CRC Press, 1994.
8. Bombardelli E, Morazzoni P. *Hypericum perforatum. Fitoterapia*, 1995, 66:43–68.

9. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
10. *Pharmacopoea Helvetica*, 8th ed. Berne, Département fédéral de l'intérieur, 1997.
11. *Pharmacopée française*. Paris, Adrapharm, 1996.
12. Piperopoulos G et al. Determination of naphthodianthrones in plant extracts from *Hypericum perforatum* L. by liquid chromatography–electrospray mass spectrometry. *Journal of Chromatography B: Biomedical Applications*, 1997, 695:309–316.
13. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
14. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
15. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
16. Brolis M et al. Identification by high-performance liquid chromatography-diode array detection-mass spectrometry and quantification by high performance liquid chromatography–UV absorbance detection of active constituents of *Hypericum perforatum. Journal of Chromatography A*, 1998, 825:9–16.
17. Nahrstedt A, Butterweck V. Biologically active and other chemical constituents of the herb of *Hypericum perforatum* L. *Pharmacopsychiatry*, 1997, 30:129–134.
18. *International statistical classification of diseases and related health problems*, *Tenth revision* (*ICD-10*), *Volume 1*. Geneva, World Health Organization, 1992.
19. Ernst E. St John's wort, an antidepressant? A systematic, criteria-based review. *Phytomedicine*, 1995, 2:67–71.
20. Laakmann G et al. St John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry*, 1998, 31 (Suppl. 1):S54–S59.
21. Linde K et al. St John's wort for depression – an overview and meta-analysis of randomized clinical trials. *British Medical Journal*, 1996, 313:253–258.
22. Maisenbacher HJ et al. Therapie von Depressionen in der Praxis. Ergebnisse einer Anwendungsbeobachtung mit Hyperici herba. *Natura Medica*, 1992, 7:394–399.
23. Pieschl D et al. Zur Behandlung von Depressionen. Verblindstudie mit einem pflanzlichen Extrakt Johanniskraut. *Therapiewoche*, 1989, 39:2567–2571.
24. Schrader E et al. *Hypericum* treatment of mild–moderate depression in a placebo-controlled study. A prospective, double-blind, randomized, placebo-controlled, multicentre study. *Human Psychopharmacology*, 1998, 13:163–169.
25. Schultz H, Jobert M. Effects of *Hypericum* extract on the sleep EEG in older volunteers. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S39–S43.

26. Schultz H et al. Clinical trials with phyto-psychopharmacological agents. *Phytomedicine*, 1997, 4:379–387.
27. Volz HP. Controlled clinical trials of *Hypericum* extracts in depressed patients – an overview. *Pharmacopsychiatry*, 1997, 30:72–76.
28. Vorbach EU, Arnoldt KH, Hübner W-D. Efficacy and tolerability of St John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD-10. *Pharmacopsychiatry*, 1997, 30:81–85.
29. Wheatley D. LI 160, an extract of St John's wort, versus amitriptyline in mildly to moderately depressed outpatients – a controlled 6-week clinical trial. *Pharmacopsychiatry*, 1997, 30:77–80.
30. Wheatley D. *Hypericum* extract: potential in the treatment of depression. *CNS Drugs*, 1998, 9:431–440.
31. Woelk H et al. Benefits and risks of the *Hypericum* extract LI 160: drug-monitoring study with 3250 patients. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S34–S38.
32. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
33. Ivan H. Preliminary investigations on the application of *Hypericum perforatum* in herpes therapy. *Gyogyszereszet*, 1979, 23:217–218.
34. Öztürk Y. Testing the antidepressant effects of *Hypericum* species on animal models. *Pharmacopsychiatry*, 1997, 30:125–128.
35. Okpanyi SN, Weischer ML. Tierexperimentelle Untersuchungen zur psychotropen Wirksamkeit eines Hypericum-Extraktes. *Arzneimittel-Forschung*, 1987, 37:10–13.
36. Öztürk Y et al. Effects of *Hypericum perforatum* L. and *Hypericum calycinum* L. extracts on the central nervous system in mice. *Phytomedicine*, 1996, 3:139–146.
37. Chatterjee SS et al. Hyperforin as a possible antidepressant component of *Hypericum* extracts. *Life Sciences*, 1998, 63:499–510.
38. Bhattacharya SK, Chakrabaarti A, Chatterjee SS. Activity profiles of two hyperforin-containing *Hypericum* extracts in behavioral models. *Pharmacopsychiatry*, 1998, 31 (Suppl. 1):S22–S29.
39. Dimpfel W et al. Effects of a methanolic extract and a hyperforin-enriched CO_2 extract of St John's wort (*Hypericum perforatum*) on intracerebral field potentials in the freely moving rat. *Pharmacopsychiatry*, 1998, 31 (Suppl. 1):S30–S35.
40. Butterweck V et al. Effects of the total extract and fractions of *Hypericum perforatum* in animal assays for antidepressant activity. *Pharmacopsychiatry*, 1997, 30:117–124.
41. Girzu M et al. Sedative activity in mice of a hydroalcohol extract of *Hypericum perforatum* L. *Phytotherapy Research*, 1997, 11:395–397.
42. Mülder H, Zöller M. Antidepressive Wirkung eines auf den Wirkstoffkomplex Hypericin standardisierten *Hypericum*-Extrakts. Bioche-

mische und klinische Untersuchungen. *Arzneimittel-Forschung*, 1984, 34:918–920.
43. Müller WE, Rossol R. Effects of *Hypericum* extract on the expression of serotonin receptors. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S63–S64.
44. Neary JT, Bu YR. *Hypericum* LI 160 inhibits uptake of serotonin and norepinephrine in astrocytes. *Brain Research*, 1999, 816:358–363.
45. Perovic S, Müller WEG. Pharmacological profile of *Hypericum* extract: effect on serotonin uptake by postsynaptic receptors. *Arzneimittel-Forschung*, 1995, 45:1145–1148.
46. Müller WE et al. Effects of *Hypericum* extract LI 160 on neurotransmitter uptake systems and adrenergic receptor density. *Second International Congress on Phytomedicine*, Munich, 1996.
47. Cott J, Misra R. Medicinal plants: a potential source for new psychotherapeutic drugs. In: Kanba S et al., eds. *New drug development from herbal medicines in neuropsychopharmacology*. New York, Brunner/Mazel Inc., 1997.
48. Wonnemann M et al. Effects of *Hypericum* extract on glutamatergic and gabaminergic receptor systems. *Pharmazie*, 1998, 53:38.
49. Chatterjee SS et al. Hyperforin inhibits synaptosomal uptake of neurotransmitters in vitro and shows antidepressant activity in vivo. *Pharmazie*, 1998, 53 (Suppl. 1):9.
50. Müller WE et al. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of *Hypericum* extract. *Pharmacopsychiatry*, 1998, 31 (Suppl. 1):16–21.
51. Baureithel KH et al. Inhibition of benzodiazepine binding in vitro by amentoflavone, a constituent of various species of *Hypericum*. *Pharmaceutica Acta Helvetiae*, 1997, 72:153–157.
52. Teufel-Mayer R, Gleitz J. Effects of long-term administration of *Hypericum* extracts on the affinity and density of the central serotonergic 5-HT_1 A and 5-HT_2 A receptors. *Pharmacopsychiatry*, 1997, 30:113–116.
53. Raffa RB. Screen of receptor and uptake-site activity of hypericin component of St John's wort reveals sigma receptor binding. *Life Sciences*, 1998, 62:PL265–PL270.
54. Suzuki O et al. Inhibition of monoamine oxidase by isogentisin and its 3*O*-glucoside. *Biochemical Pharmacology*, 1978, 27:2075–2078.
55. Suzuki O et al. Inhibition of type A and type B monoamine oxidase by naturally occurring xanthones. *Planta Medica*, 1981, 42:17–21.
56. Suzuki O et al. Inhibition of monoamine oxidase by hypericin. *Planta Medica*, 1984, 50:272–274.
57. Hölzl J et al. Investigation about antidepressive and mood-changing effects of *Hypericum perforatum*. *Planta Medica*, 1989, 55:643.
58. Demisch L et al. Identification of selective MAO type A inhibitors in *Hypericum perforatum* L. (Hyperforat®). *Pharmacopsychiatry*, 1989, 22:194.

59. Sparenberg B et al. Untersuchungen über antidepressive Wirkstoffe von Johanniskraut. *Pharmazie Zeitschrift Wissenschaften*, 1993, 138:50.
60. Höltje HD, Walper A. Molecular modeling of the antidepressive mechanism of *Hypericum* ingredients. *Nervenheilkunde*, 1993, 12:339–340.
61. Bladt S, Wagner H. Inhibition of MAO by fractions and constituents of *Hypericum* extract. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S57–S59.
62. Thiede HM, Walper A. Inhibition of MAO and COMT by *Hypericum* extracts and hypericin. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S54–S56.
63. Thiele B et al. Modulation of cytokine expression by *Hypericum* extract. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S60–S62.
64. Itokawa H et al. Studies on the constituents of crude drugs having inhibitory activity against contraction of the ileum caused by histamine or barium chloride. I. Screening test for the activity of commercially available crude drugs and the related plant materials. *Shoyakugaku Zasshi*, 1983, 37:223–228.
65. Zaitseva IM. The effect of common St John's wort on the gastrointestinal system. *Zdravookhr Beloruss*, 1966, 12:23.
66. Melzer R et al. Vasoactive properties of procyanidins from *Hypericum perforatum* L. in isolated porcine coronary arteries. *Arzneimittel-Forschung*, 1991, 41:481–483.
67. Barbagallo C, Chisari G. Antimicrobial activity of three *Hypericum* species. *Fitoterapia*, 1987, 58:175–177.
68. May G, Willuhn G. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. *Arzneimittel-Forschung*, 1978, 28:1–7.
69. Mishenkova EL et al. Antiviral properties of St John's wort and preparations produced from it. *Trudy S'ezda mikrobiologii Ukrainskoi*, 1975, 4:222.
70. Pacheco P et al. Antiviral activity of Chilean medicinal plant extracts. *Phytotherapy Research*, 1993, 7:415–418.
71. Anderson DO et al. In vitro virucidal activity of selected anthraquinones and anthraquinone derivatives. *Antiviral Research*, 1991, 162:185–196.
72. Carpenter S, Kraus GA. Photosensitization is required for inactivation of equine infectious anemia virus by hypericin. *Photochemistry and Photobiology*, 1991, 53:169–174.
73. Hudson JB et al. Antiviral assays on phytopharmaceuticals: the influence of reaction parameters. *Planta Medica*, 1994, 604:329–332.
74. Lavie G et al. Hypericin as an antiretroviral agent. Mode of action and related analogues. *Annals of the New York Academy of Sciences*, 1992:556–562.
75. Lopez-Bazzocchi I et al. Antiviral activity of the photoactive plant pigment hypericin. *Photochemistry and Photobiology*, 1991, 54:95–98.
76. Moraleda G et al. Inhibition of duck hepatitis B virus replication by hypericin. *Antiviral Research*, 1993, 20:223–247.

77. Wood S et al. Antiviral activity of naturally occurring anthraquinones and anthraquinone derivatives. *Planta Medica*, 1990, 56:651–652.
78. Cohen PA et al. Antiviral activities of anthraquinones, bianthrones and hypericin derivatives from lichens. *Experientia*, 1996, 523:180–183.
79. Degar S et al. Inactivation of the human immunodeficiency virus by hypericin: evidence for photochemical alterations of p24 and a block in uncoating. *AIDS Research and Human Retroviruses*, 1992, 8:1929–1936.
80. Lavie G et al. Studies of the mechanisms of action of the antiretroviral agents hypericin and pseudohypericin. *Proceedings of the National Academy of Sciences of the United States of America*, 1989, 86:5963–5967.
81. Meruelo D et al. Therapeutic agents with dramatic antiretroviral activity and little toxicity at effective doses: aromatic polycyclic diones hypericin and pseudohypericin. *Proceedings of the National Academy of Sciences of the United States of America*, 1988, 85:5230–5234.
82. Tang J et al. Virucidal activity of hypericin against enveloped and nonenveloped DNA and RNA viruses. *Antiviral Research*, 1990, 136:313–325.
83. Weber ND et al. The antiviral agent hypericin has in vitro activity against HSV-1 through non-specific association with viral and cellular membranes. *Antiviral Chemistry and Chemotherapy*, 1994, 5:83–90.
84. Schinazi RF et al. Anthraquinones as a new class of antiviral agents against human immunodeficiency virus. *Antiviral Research*, 1990, 135:265–272.
85. Fokina GI et al. Experimental phytotherapy of tick-borne encephalitis. *Soviet Progress in Virology*, 1991, 1:27–31.
86. Lenard J et al. Photodynamic inactivation of infectivity of human immunodeficiency virus and other enveloped viruses using hypericin and Rose bengal: inhibition of fusion and syncytia formation. *Proceedings of the National Academy of Sciences of the United States of America*, 1993, 901:158–162.
87. Agostinis P et al. Photosensitized inhibition of growth factor-regulated protein kinases by hypericin. *Biochemical Pharmacology*, 1995, 4911:1615–1622.
88. Agostinis P et al. A comparative analysis of the photosensitized inhibition of growth factor-regulated protein kinases by hypericin derivatives. *Biochemical and Biophysical Research Communications*, 1996, 2203:613–617.
89. De Witte PA et al. Inhibition of epidermal growth factor receptor tyrosine kinase activity by hypericin. *Biochemical Pharmacology*, 1993, 46:1929–1936.
90. Lavie G et al. The chemical and biological properties of hypericin A compound with a broad spectrum of biological activities. *Medical Research Reviews*, 1995, 152:111–119.
91. Samel D, De Witte P. Selective inhibition of PK-C activity by *Fagopyrum esculentum* extract. *Phytotherapy Research*, 1996, 10 (Suppl. 1):S156–S158.
92. Zhang W et al. Enhancement of radiosensitivity in human malignant glioma cells by hypericin in vitro. *Clinical Cancer Research*, 1996, 25:843–846.
93. Couldwell WT et al. Hypericin: a potential antiglioma therapy. *Neurosurgery*, 1994, 35:705–710.

94. Panossian AG et al. Immunosuppressive effects of hypericin on stimulated human leucocytes: inhibition of the arachidonic acid release, leukotriene B_4 and interleukin-1α production and activation of nitric oxide formation. *Phytomedicine*, 1996, 3:19–28.
95. Fedorchuk AM. Effect of *Hypericum perforatum* on experimentally infected wounds. *Mikrobiologichnii Zhurnal (Kiev)*, 1964, 26:32.
96. Lazareva KN et al. The results of a study of some drug plants of the Bashkir USSR. *Sbornik Nauchnykh Trudov Bashkir Gosudarstvennogo Meditsinskii Institut*, 1968, 17:54.
97. Rao SG et al. *Calendula* and *Hypericum*: two homeopathic drugs promoting wound healing in rats. *Fitoterapia*, 1991, 62:508–510.
98. Daniel K. Kurze Mitteilung über 12 jährige therapeutische Erfahrungen mit Hypericin. *Klinische Wochenschrift*, 1951, 29:260–262.
99. Schakau D et al. Risk/benefit profile of St John's wort extract. *Psychopharmakotherapie*, 1996, 3:116–122.
100. Kugler J et al. Therapie depressiver Zustände. *Hypericum*-Extrakt Steigerwald als Alternative zur Benzodiazepin-Behandlung. *Zeitschrift für Allgemeine Medizin*, 1990, 66:21–29.
101. Demisch L et al. Einfluss einer subchronischen Gabe von Hyperforat auf die nächtliche Melatonin- und Kortisolsekretion bei Probanden. Nürnberg, Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie Symposium Abstract 1991.
102. *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington, DC, American Psychiatric Association, 1994.
103. Schellenberg R et al. Pharmacodynamic effects of two different *Hypericum* extracts in healthy volunteers measured by quantitative EEG. *Pharmacopsychiatry*, 1998, 31 (Suppl. 1):S44–S53.
104. Johnson D. Neurophysiologische Wirkungen von *Hypericum* im Doppelblindversuch mit Probanden. *Nervenheilkunde*, 1991, 10:316–317.
105. Johnson D et al. Effects of *Hypericum* extract LI 160 compared with maprotiline on resting EEG and evoked potentials in 24 volunteers. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S44–S46.
106. Martinez B et al. *Hypericum* in the treatment of seasonal affective disorders. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S29–S33.
107. Kasper S. Treatment of seasonal affective disorder (SAD) with *Hypericum* extract. *Pharmacopsychiatry*, 1997, 30 (Suppl. 1):S89–S93.
108. Staffeldt B et al. Pharmacokinetics of hypericin and pseudohypericin after oral intake of the *Hypericum perforatum* extract LI 160 in healthy volunteers. *Journal of Geriatric Psychiatry and Neurology*, 1994, 7 (Suppl. 1):S47–S53.
109. Brockmöller J et al. Hypericin and pseudohypericin: pharmacokinetics and effects on photosensitivity in humans. *Pharmacopsychiatry*, 1997, 30:94–101.
110. Biber A et al. Oral bioavailability of hyperforin from *Hypericum* extracts in rats and human volunteers. *Pharmacopsychiatry*, 1998, 31 (Suppl. 1):S36–S43.

111. Konig CD. *Hypericum perforatum L. (gemeines Johanniskraut) als Therapeutikum bei depressiven Verstimmungszuständen—eine Alternative zu synthetischen Arzneimitteln?* [Dissertation]. Basel, University of Basel, 1993.
112. Cott JM. In vitro receptor binding and enzyme inhibition by *Hypericum perforatum* extract. *Pharmacopsychiatry*, 1997, 30 (Suppl. 1):S108–S112.
113. Nebel A et al. Potential metabolic interaction between St John's wort and theophylline. *Annals of Pharmacotherapy*, 1999, 33:502.
114. Johne A et al. Interaction of St John's wort extract with digoxin. In: *Jahreskongress für klinische Pharmakologie*. Berlin, 1999.
115. Ernst E. Second thoughts about safety of St John's wort. *Lancet*, 1999, 354: 2014–2016.
116. Lantz MS, Buchalter E, Giambanco V. St John's wort and antidepressant drug interactions in the elderly. *Journal of Geriatric Psychiatry and Neurology*, 1999, 12:7–10.
117. Piscitelli SC et al. Indinavir concentrations and St John's wort. *Lancet*, 2000, 355:547–548.
118. Okpanyi SN et al. Genotoxizität eines standardisierten *Hypericum* Extrakts. *Arzneimittel-Forschung*, 1990, 40:851–855.
119. Poginsky B et al. Johanniskraut (*Hypericum perforatum* L.). Genotoxizität bedingt durch den Quercetingehalt. *Deutsche Apotheker Zeitung*, 1988, 128:1364–1366.
120. Schimmer O et al. The mutagenic potencies of plant extracts containing quercetin in *Salmonella typhimurium* TA 98 and TA 100. *Mutation Research*, 1988, 206:201–208.
121. Schimmer O et al. An evaluation of 55 commercial plant extracts in the Ames mutagenicity test. *Pharmazie*, 1994, 49:448–451.
122. Leuschner J. Preclinical toxicological profile of *Hypericum* extract LI 160. *Second International Congress on Phytomedicine*. Munich, 1996.
123. Siegers CP et al. Zur Frage der Phototoxizität von *Hypericum*. *Nervenheilkunde*, 1993, 12:320–322.
124. Roots I et al. Evaluation of photosensitization of the skin upon single and multiple dose intake of *Hypericum* extract. In: *Second International Congress on Phytomedicine*. Munich, 1996.
125. Golsch S et al. Reversible Erhöhung der Photosensitivität im UV-B-Bereich durch Johanniskrautextrakt-Präparate. *Hautarzt*, 1997, 48:249–252.
126. Bove GM. Acute neuropathy after exposure to sun in a patient treated with St John's wort. *Lancet*, 1998, 352:1121.
127. Herberg KW. Psychotrope Phytopharmaka im Test. Alternative zu synthetischen Psychopharmaka? *Therapiewoche*, 1994, 44:704–713.
128. Schmidt U et al. Johanniskraut-Extrakt zur ambulanten Therapie der Depression. Aufmerksamkeit und Reaktionsvermögen bleiben erhalten. *Fortschritt der Medizin*, 1993, 111:339–342.

Herba Leonuri

Definition

Herba Leonuri consists of the whole or cut, dried flowering aerial parts of *Leonurus cardiaca* L. (Lamiaceae) (*1*). According to the *USSR Pharmacopoeia*, Herba Leonuri consists of the whole or cut, dried aerial parts of *L. cardiaca* L. (*L. cardiaca* L. subsp. *villosus* (Desf.) Jav.) and *L. quinquelobatus* Gilib., collected at the beginning of flowering (*2*).

Synonyms

Cardiaca trilobata Lam., *C. vulgaris* Moench, *Lamium cardiaca* (L.) Baill., *Leonurus campestris* Andrz., *L. canescens* Dumort, *L. glaucescens* Ledeb., *L. tataricus* L., *L. villosus* Desf. ex Spreng., *L. trilobatus* (Lam.) Dulac (*3–5*).

Selected vernacular names

Agrimaume, agripalma, agripaume, agripoume cardiaque, äkta hjärtstilla, arslan kuyruğu, arslonkuiruk, baqlat el amhât, bonässla, bärenschweif, cardiaca, cardiaco, cardiaque, coda di leone, common motherwort, common mother-wort, dom-e-shir, echtes Herzgespann, farâsîyûn el qalb, farasyun kalbi, five-lobed bladderwort, herbe battudo, Herzgespann, hjärtstilla, kalomiro, leonuro, lion's ear, lion's tail, lääne-südamerohi, Löwenschwanz, melissa salvatica, motherwort, Mutterwurz, nukula, pust'rnik serdechn'i, qafil, roman motherwort, serdetshn'i, shavbalaha, sidrs mātere, talpa gâştii, throwwort, throw-wort, tsan-ts'ai, wolfstrapp, yabani pirasa, yi-mu-ts,ao (*4*, *6*, *15*).

Geographical distribution

Indigenous to central and eastern Europe and Scandinavia and Central Asia; also found in Caucasia and western Siberia. It was introduced to North America and has become established in the wild. It is also cultivated (*4*, *6*, *16–21*).

Description

A perennial plant, 50–120(200) cm high, short woody rhizome. Stem erect, quadrangular, grooved, hollow, pale green or purplish brown, often

red-violet, may have short hairs on the corners (*L. quinquelobatus* has long prominent hairs on the stem). Leaves decussate, pubescent or glabrous, upper surface green, smooth, lower surface paler and markedly pubescent (veins on the underside of *L. quinquelobatus* leaves are covered by prominent hairs). Leaves, blades broadly ovate to nearly circular in outline, long-petiolated, irregular serrate margin, acute apex, 7–12 cm long; lower leaves 5–7 palmatisect; medium leaves 3-lobed or entire; upper leaves elliptical, ovate base, with two prominent lateral dents, petiole 1–2 cm long (*L. quinquelobatus* has 3-palmatisect or 3-lobed leaves, rarely entire). Inflorescence, long, spike-like, formed by verticillasters of 6–12 small flowers in the axils of the upper leaves. Bracts subulate, short-haired (*L. quinquelobatus* has prominent hairs on the bracts). Calyx green, 5–6 mm long, funnel-shaped, with 5 equal pointed sepals (their triangular apexes are 3–3.5 mm long; two of them are turned down). Corolla 2-lipped, longer than calyx, pink to whitish with purple spots on the 3-lobed lower lip; upper lip entire, hairy on the upper surface (sometimes the upper lip of *L. cardiaca* is glabrous). Stamens 4, under upper lip, stigma 2-lobed. Fruit, triangular nutlet with a tuft of hairs at the tip, brown, 2.5–3 mm long (*6*, *16*, *22–27*).

Plant material of interest: dried aerial parts

General appearance

The stem pieces are hairy, longitudinally striated, quadrangular, hollow, up to about 10 mm wide. They bear decussate, opposite, petiolate leaves and about 6–12 flowers, arranged in sessile whorls forming a long leafy spike. The leaves are ovate-orbicular, palmately 3–5-lobed, rarely 7-lobed, the lobes irregularly dentate. The upper surface of the leaves is green with scattered hairs, the lower surface is paler green, densely pubescent and shows a prominent palmate and reticulate venation. The flowers have a funnel-shaped calyx, 3–5 mm long with stiff, recurved teeth; the corolla is 2-lipped, the upper lip pink and pubescent on the outer surface, the lower lip white with purplish spots; stamens 4, densely pubescent (*1*).

Organoleptic properties

Odour: strongly aromatic; taste: bitter (*28*).

Microscopic characteristics

Stem: transverse section shows stem ridged, four-angled with a central hollow; epidermal cells longitudinally elongated with occasional diacytic and anomocytic stomata, and numerous non-glandular trichomes; cover-

ing trichomes, uniseriate, composed of 2–8 cells with slight swellings at the junctions and thick warty walls; glandular trichomes of the typical Lamiaceae type with a short, unicellular stalk and a head composed of a single cell, or less frequently, multicellular and rounded, composed of 4–8 cells; cortex narrow, parenchymatous with collenchyma at the ridges; phloem narrow, thin-walled; xylem lignified with small, spirally and annularly thickened vessels and groups of thick-walled fibres. Leaf: upper epidermal cells of leaf straight-walled with a striated cuticle and scattered large, rounded, diacytic and anomocytic stomata; lower epidermal cells with sinuous walls and more numerous stomata; abundant covering and glandular trichomes on both surfaces, particularly on the lower surface, similar to those occurring on the stem, with both types of glandular trichomes equally numerous. Flower: epidermal cells of the calyx with sinuous anticlinal walls; mesophyll cells containing numerous small cluster crystals of calcium oxalate; inner epidermis of the corolla with very numerous covering trichomes similar to those occurring on the stem and leaves; fibrous layer of the anther; pollen grains spherical, about 25–30 µm in diameter, with 3 pores and 3 furrows and a smooth exine; occasional brown fragments of pericarp with single crystals of calcium oxalate (*1*, *2*, *28*, *29*).

Powdered plant material

Greenish-grey powder with a strong, aromatic odour and a bitter taste. The powder has the same microscopic characteristics as the entire stem, leaf and flower (see Microscopic characteristics) (*28*).

General identity tests

Macroscopic and microscopic examinations, luminescence microscopy and thin-layer chromatography for the characteristic constituents, iridoids and flavonoids (*1*, *2*, *5*, *28*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*30*).

Chemical

No information available.

Foreign organic matter

Maximum 2% of brownish or yellowish leaves and maximum 2% other foreign matter (*1*, *28*). Not more than 3% of foreign organic matter. Not more than 46% of stems. Not more than 7% of blackish, brownish and yellowish parts of plant. For cut drug: not more than 17% of fragments having a diameter of more than 7 mm; not more than 16% of fragments having a diameter of less than 0.5 mm (*2*).

Total ash

Not more than 12% (*1*, *2*, *28*).

Acid-insoluble ash

Ash insoluble in hydrochloric acid not more than 2% (*28*). Ash insoluble in 10% hydrochloric acid not more than 6% (*2*).

Sulfated ash

No information available.

Water-soluble extractive

Not less than 15% (*28*).

Alcohol-soluble extractive

Extractive soluble in 70% ethanol not less than 15% (*2*).

Loss on drying

Not more than 12% (*1*). Not more than 13% (*2*).

Pesticide residues

The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*1*). For other pesticides, see the *European pharmacopoeia* (*1*) and the WHO guidelines on quality control methods for medicinal plant materials (*30*) and pesticide residues (*31*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*30*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*30*) for the analysis of radioactive isotopes.

Other purity tests

Content of mineral matter not more than 1% (*2*). Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 0.2% of total flavonoids, expressed as hyperoside (*1*).

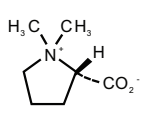
Major chemical constituents

The major constituents of the aerial parts are flavonoids: *O*-glycosides of quercetin (including rutin, quercitrin, isoquercitrin, hyperoside), of kaempferol and of apigenin. Also present are the apigenin derivatives genkwanin and quinqueloside, the alkaloids ((–)-stachydrine and leonurine), iridoid glucosides (leonuride, ajugol, galiridoside and reptoside), diterpenoids (leocardin, mixture of 2 clerodane derivatives), cycloleonuripeptides (A, B, C and D), triterpenes (ursolic acid), bitter glycosides, caffeic acid 4-rutinoside and tannins (*4*, *6*, *16–19*, *32–39*). The structures of the characteristic constituents are presented below.

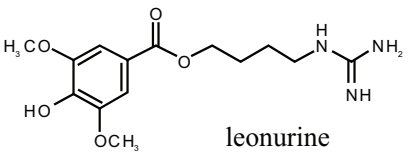
Medicinal uses

Uses supported by clinical data

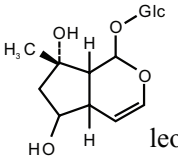
Positive cardiovascular effects have been reported in open clinical trials (*41*, *42*).



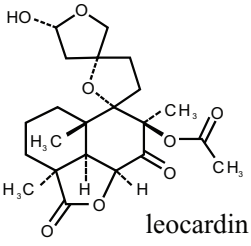
stachydrine



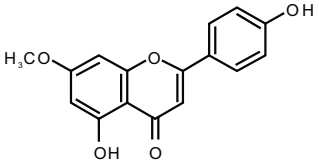
leonurine



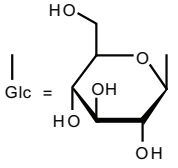
leonuride



leocardin



genkwanin



β-D-glucopyranosyl

Uses described in pharmacopoeias and well established documents

Herba Leonuri is used against cerebral ischaemia (*32*). It is also used for treatment of heart palpitations occurring with anxiety attacks or other nervous disorders (*6*, *43–45*).

Uses described in traditional medicine

Traditionally, Herba Leonuri has been used for certain types of heart conditions, simple tachycardia, effort syndrome, and specifically for cardiac symptoms associated with neurosis (*28*). Herba Leonuri has also been used for urine stimulation, and for removing calculus from kidneys. Used as a remedy for female reproductive disorders; the plant stimulates the muscles of the uterus and is used to treat delayed menstruation, menstrual pain and premenstrual tension (*46*).

Pharmacology

Experimental pharmacology

Cardiovascular effects

An extract of the dried entire plant has demonstrated antihypertensive activity in rats when administered by intravenous injection at a dose of 50 mg/kg body weight (bw) (*47*). The effects of aqueous extracts of Herba Leonuri on the contractility of isolated rat aorta were investigated in vitro. Although the aqueous extract (0.3–3 mg/ml) by itself had a limited effect, the extract enhanced phenylephrine-induced contraction of aorta with endothelium. This effect was not seen in studies on the aorta without endothelium. The aqueous extract, like nitro-L-arginine methyl ester, an inhibitor of nitric oxide synthase, significantly inhibited the relaxation induced by acetylcholine in the aorta with endothelium ($p < 0.05$). Coadministration of the extract with 1 mM of L-arginine reduced the inhibitory effect of the extract on the relaxation of aorta. The vasoconstrictive effect of the extract was not due to leonurine, a constituent of Herba Leonuri, which expressed uterotonic activity. Intravenous injection of the aqueous extract (1.5 mg/kg bw) to rats produced an increase in blood pressure for 5 minutes, similar to that produced by nitro-L-arginine methyl ester (1.35 mg/kg bw). These findings suggest that there is a constituent of Herba Leonuri, which has vasoconstrictive activity in the rat, both in vitro and in vivo, with a similar pharmacological profile to nitro-L-arginine methyl ester (*48*).

Antioxidant effects

Using antioxidant assays employing 2,2´-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) and diphenyl-l-picrylhydrazyl in vitro, it was

demonstrated that in addition to elevating endogenous antioxidant enzyme activity, Herba Leonuri, used traditionally in Chinese herbal medicine for the treatment of cardiovascular disorders, contains a potent antioxidant component capable of effective inhibition of oxidative reactions mediated by the inflammatory oxidants, peroxynitrite, hypochlorous acid and hydroxyl radicals, as well as iron-dependent lipid peroxidation (*49*).

The antioxidant and cardioprotective effects of an extract of Herba Leonuri on ischaemic myocardium were investigated in rats. A daily dose of the extract (400 mg/kg bw per day) was administered orally starting from 1 week before and continuing until 3 weeks after myocardial infarction. Surviving rats were killed at different times to obtain left ventricles for biochemical assays. The results demonstrated for the first time that Herba Leonuri has antioxidant effects both in vitro and in vivo. The antioxidant effects of the extract are exerted only under the condition of oxidative stress, by selectively preserving the activities of superoxide dismutase and glutathione peroxidase, as well as depressing the formation of malondialdehyde. Its effects of scavenging free radicals and inhibiting the formation of reactive oxygen species probably play a role in protecting the endogenous antioxidant system from oxidative stress in vivo (*50*).

Antitumour activity

Herba Leonuri demonstrated cytotoxicity during in vitro studies on lymphocytic leukaemia (P-388, L-1210), KB cells, human lung carcinoma (A-549), mammary tumour (MCF-7) and human colon tumour cells (HCT-8) (*51*). Ingestion of the methanol extract of Herba Leonuri in drinking-water at a concentration of 0.5% markedly suppressed the development of mammary cancers in multiparous GR/A mice. The incidence of uterine adenomyosis was also inhibited in mice given an extract of Herba Leonuri. The stimulation by the extract of the excretion of any carcinogenic factors may at least partly contribute to its inhibition of mammary cancers (*52*).

Toxicology

No documented toxicity studies were found, but ursolic acid has been reported to have cytotoxic activity (*51*). A median lethal dose for the extract of Herba Leonuri in rats of 10.8 g/kg bw by intraperitoneal injection has been recorded (*47*). In the USA, Herba Leonuri is listed by the US Food and Drug Administration as a "herb of undefined safety" (*53*).

Clinical pharmacology

A 70% ethanol extract of Herba Leonuri was tested in an open clinical study in patients with cardiovascular diseases. An improvement in cardiac activity, and a reduction in blood pressure was observed in 69% of patients (*41*).

The effect of Herba Leonuri on blood hyperviscosity was investigated in 105 patients. An extract of Herba Leonuri, 10 ml (5 g/ml) in 250 ml of 5% glucose, was given once daily intravenously for 15 days. In 94.5% of patients, improvement was observed. The researchers noted a decrease in blood viscosity and in fibrinogen volume, an increase in the deformability of red blood cells, and a decrease in platelet aggregation (*42*).

In an open controlled study 121 normal fertile women were given an oral dose of a decoction of Herba Leonuri (30 g dry weight equivalent). An increase in intrauterine pressure in 41.3% of the women was demonstrated. The increase ranged from 150% to more than 300% of spontaneous activity before dosing. Intramuscular injection of ergonovine (positive control) at a dose of 0.2 mg produced a 1% increase in intrauterine pressure. A blind control with water yielded a positive response rate of 2.7%. There were no observable side-effects reported apart from diuresis (*54*).

The efficacy of several plants (*Valeriana*, *Leonurus*, *Aralia*, *Hypericum*, *Echinopanax*, *Eleutherococcus*, *Schizandra*, and *Panax ginseng*) as photoprotectors and photosensitizers was tested by assessing the influence of their extracts on the photochemiluminescence of glycyl-tryptophan solutions. Photosensitization was studied under irradiation with light $\lambda > 280$ nm, as well as with monochromatic light $\lambda = 313$, 365, 405 and 436 nm. All of the plants studied acted as photoprotectors at low concentrations and as photosensitizers at high concentrations. The efficiency of photoprotection or photosensitization of a single dose of plant extracts and their concentration in humans were determined. In order of decreasing effect, the sequence was as follows: *Leonurus* > *Hypericum* > *Aralia* > *Schizandra* > *Echinopanax* > *Eleutherococcus* > *Valeriana* > *Panax ginseng*. Photosensitization is attributed to the components of the plant extracts which have strong absorption at high wavelengths (*55*).

Adverse reactions

No information was found.

Contraindications

Herba Leonuri should be avoided during pregnancy due to its uterotonic activity, and its ability to affect the menstrual cycle (*46*, *53*). Herba Leon-

uri is also contraindicated in individuals with arterial hypotension and bradycardia (*56*). If signs of hypersensitivity reactions appear, Herba Leonuri must not be used again (*45*).

Precautions

General

No information was found.

Drug interactions

Herba Leonuri strengthens the hypnotic effects of central nervous system depressants, and shows antagonism in relation to analeptic stimulants (*21*).

Carcinogenesis, mutagenesis, impairment of fertility

No information was found.

Pregnancy

See Contraindications.

Nursing mothers

The use of the plant during breastfeeding should be avoided (*53*).

Paediatric use

No information was found.

Dosage forms

Comminuted herb for infusions and other Galenical preparations for internal use.

Posology

(Unless otherwise indicated)

The average daily dosage is 2–4.5 g of dried herb or equivalent preparations (*28*).

For internal use. Infusion (2–4.5 g of dried herb in 150 ml boiled water for 10–15 minutes), one tablespoonful three times daily between meals (*21*). Tincture (1:5 in 45% ethanol) 2–6 ml, three times daily (*57*). Fluidextract (1:1 in 25% ethanol) 2–6 ml, three times daily (*58*).

References

1. *European pharmacopoeia*, 5th ed. Strasbourg, European Pharmacopoeia Commission, 2005.
2. *USSR pharmacopoeia*, 11th ed. *Vol. 2.* Moscow, Meditsina, 1990.
3. *Northern Ontario plant database* (http://www.northernontarioflora.ca/).
4. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific, 2001.
5. *HagerROM 2004. Hagers Handbuch der Drogen und Arzneistoffe.* Heidelberg, Springer Verlag, 2005.
6. Fleming T, ed. *Physician's desk reference (PDR) for herbal medicines*. Montvale, Medical Economics Company, 2000.
7. *Henriette's plant name search* (http://www.henriettesherbal.com/php/index.php).
8. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
9. Grigorescu E, Ciulei I, Ursula S. *Index fitoterapeutic.* Bucharest, Editura Medicala, 1986.
10. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.
11. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005 (http://www.napralert.org).
12. Mozaffarin V. *A dictionary of Iranian plant names. Latin, English, Persian*. Tehran, Farhang Mo'aser, 1998.
13. Bedevian AK. *Illustrated polyglottic dictionary of plant names*. Cairo, Medbouly Library, 1994.
14. Īriste V, Eniņa V. *Ārstniecības augu vārdnīca.* Riga, Medikamentu informācijas centers, 2000.
15. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
16. Muravjova DA. *Farmakognozija*. Moscow, Meditsina, 1991.
17. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
18. Yakovlev GP, Blinova KF, ed. *Lekarstvennoje rastitel'noje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
19. Yakovlev GP, Blinova KF, ed. *Rastenija dlja nas.* St Peterburg, Utchebnaja kniga, 1996.
20. *Plants for a future. Database* (http://www.ibiblio.org/pfaf/database/latinB.html).
21. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.
22. Komarov VL, Shishkin BK, eds. *Flora SSSR. Vol. 21. Pod red.* Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR. 1936.

23. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR. Izd.* Moscow, Mysli, 1976.
24. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR. 3-ie izd.* Kishinev, Shtiintsa, 1986.
25. *Botaniceskii atlas.* Mosva, Izdatel'stvo selskohozeaistvennoi literatury, jurnalov i plakatov, 1963.
26. Alexeev IE. *Travianistye rastenia SSSR. Vol. 2.* Moscow, Izdatelistvo Mysl', 1971.
27. *British herbal pharmacopoeia*. Exeter, British Herbal Medicine Association, 1996.
28. *British herbal pharmacopoeia. Vol. 1.* Bournemouth, British Herbal Medicine Association, 1990.
29. Toma C, Rugina R. *Anatomia plantelor medicinale. Atlas.* Bucharest, Editura Academiei Romane, 1998.
30. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
31. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
32. Bradley PR, ed. *British herbal compendium*. *Vol. 1.* Bournemouth, British Herbal Medicine Association, 1992.
33. Morita H et al. Cycloleonuripeptides A, B and C, three new proline-rich cyclic nonapeptides from *Leonurus heterophyllus*. *Bioorganic & Medicinal Chemistry Letters*, 1996, 6:767–770.
34. Rastogi RP, Mehrotra BN. *A compendium of Indian medicinal plants*. *Vol 4.* Delhi, Publications & Information Directorate, 1995.
35. *Rastitel'nye resursy SSSR*. *Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Magnoliaceae-Limoniaceae. Vol. 6.* Leningrad, Nauka, 1991.
36. Kartnig T, Gruber A, Menzinger S. Flavonoid-O-glycosides from the herbs of *Leonurus cardiaca*. *Journal of Natural Products*, 1985, 48:494.
37. Gulubov AZ, Chervenkova VB. Structure of alkaloids from *Leonurus cardiaca. Matematika, Fizika, Khimiya, Biologiya*, 1970, 8:129–132.
38. Malakov P et al. The structure of leocardin, two epimers of a diterpenoid from *Leonurus cardiaca. Phytochemistry*, 1985, 24:2341–2343.
39. Weinges K, Kloss P, Henkels WD. Natural products from medicinal plants. XVIII. Isolation and structure elucidation of a new C15-iridoid glucoside from *Leonurus cardiaca. Justus Liebigs Annalen der Chemie*, 1973, 4:566–572.
40. Buzogany K, Cucu V. Comparative study between the species *Leonurus cardiaca* L. and *Leonurus quinquelobatus* Gilib. Part II. Iridoids. *Clujul Medical*, 1983, 56:385–388.
41. Turova AD. *Lekarstvennye rastenija SSSR i ikh primenenie*. Moscow, Meditsina, 1974.
42. Zou OZ et al. Effects of motherwort on blood hyperviscosity. *American Journal of Clinical Medicine*, 1989, 17:65–70.

43. Wren RC. *Potter's new cyclopaedia of botanical drugs and preparations.* Essex, CW Daniel, 1988.
44. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
45. Newall CA et al., eds. *Herbal medicines. A guide for health-care professionals*. London, Pharmaceutical Press, 1996.
46. Chevallier A. *The encyclopedia of medicinal plants*. London, Dorling Kindersley, 1996.
47. Racz-Kotilla E, Racz G, Bartha R. Antihypertensive action of *Leonurus quinquelobatus* and *L. turkestanicus* extracts. *Review of Medicine,* 1981, 27:32–35.
48. Pang S et al. Enhancement of phenylephrine-induced contraction in the isolated rat aorta with endothelium by H_2O-extract from an Oriental medicinal plant Leonuri Herba. *Japanese Journal of Pharmacology*, 2001, 86:215–222.
49. Zhu YZ et al. Antioxidants in Chinese herbal medicines: a biochemical perspective. *Natural Product Reports,* 2004, 21:478–489.
50 Sun J et al. Anti-oxidative stress effects of Herba Leonuri on ischemic hearts. *Life Sciences*, 2005, 76:3043–3056.
51. Kuo-Hsiung L et al. The cytotoxic principles of *Prunella vulgaris, Psychotria serpens,* and *Hyptis capitata*: Ursolic acid and related derivatives. *Planta Medica,* 1988, 54:308–311.
52. Nagasawa H et al. Effects of motherwort (*Leonurus sibiricus* L) on preneoplastic and neoplastic mammary gland growth in multiparous GR/A mice. *Anticancer Research*, 1990, 10:1019–1023.
53. Duke JA et al. *Handbook of medicinal herbs*. Boca Raton, FL, CRC Press, 1985.
54. Chan WC et al. Clinical observation on the uterotonic effect of I-mu Ts'ao (*Leonurus artemisia*). *American Journal of Clinical Medicine*, 1983, 11:77–83.
55. Bol'shakova IV, Losovskaia EL, Sapezhinskii II. Photosensitizing and photoprotective properties of extracts from groups of medicinal plants. *Biofizika*, 1997, 42:926–932.
56. Ladynina EA, Morozova RS. *Fitoterapija*. Leningrad, Meditsina, 1987.
57. Lager AA. *Fitoterapija*. Krasnojarsk, Izdatel'stvo krasnojarskogo universiteta, 1988.
58. Barnes J et al., eds. *Herbal medicines. A guide for healthcare professionals*. London, Pharmaceutical Press, 2002.

Folium Melissae

Definition
Folium Melissae consists of the dried leaves of *Melissa officinalis* L. (Lamiaceae, Labiatae) (*1*, *2*).

Synonyms
Calamintha officinalis Moench. (*3*), *Melissa graveolens* Host, *Thymus melissa* E.H.L. Krause (*4*). Lamiaceae is also referred to as Labiatae.

Selected vernacular names
Alahana, appiastro, badarendjabouya, badranjbuyeh, balm, balm mint, bee balm, blue balm, cedronella, citromfülevél, citronelle, citrounado, citrounela, citrounelo, common balm, cure-all, dropsy plant, erva-cidreira-miudade-folha, folia citronellae, franjmeshk, garden-balm, Herzkraut, hhashyshat ennahhl, honey plant, lemon balm, limiera, limouna, limounneta, mallisa, melissa, Melisse, Melissenblätter, Melissenkraut, melisso, melliss, ponciarada, pouncinado, sidrunmeliss, sweet balm, toronjil, toronjil-cidrado, touroudjan, turungan, Zitronenkraut, Zitronenmelisse (*4*–*8*).

Geographical distribution
Indigenous to western Asia and the eastern Mediterranean region, and is cultivated in central, eastern and western Europe, and the United States of America (*4*, *7*, *8*).

Description
An odorous perennial herb, 0.3–0.9 m high, usually with several stems, lemon-scented on bruising. Stems obtusely quadrangular, furrowed pubescent. Leaves 2–9 cm long and 1–5 cm wide, ovate to obovate-oval, base cuneate truncate or cordate at the base, densely pilose on both surfaces, petiole 0.2–3.5 cm long. Corolla white or pinkish; infundibuliform tube 8–12 mm long; stamens inserted deep in the tube; bracteoles oval-oblong, about 1.5 cm long, pubescent; calyx 5–9 mm long, pubescent outside, pubescent inside (with very short hairs), densely pilose in the middle (*4*, *8*, *9*).

Plant material of interest: dried leaves

General appearance

Leaves oval, cordate, up to about 8 cm long and 5 cm wide, with more or less long petioles; lamina thin, lower surface has conspicuous, raised, reticulate venation; margins roughly dentate or crenate; upper surface bright green, lower surface lighter in colour (*1*).

Organoleptic properties

Odour: aromatic, lemon-like; taste: aromatic, lemon-like (*1*).

Microscopic characteristics

Dorsoventral epidermal cells with sinuous walls and diacytic stomata on lower surface only; very short, conical, unicellular covering trichomes with a finely striated cuticle occur abundantly, especially over the veins on the lower surface; also uniseriate, multicellular (2–5 cells) covering trichomes, wide at the base and narrowing rapidly toward the tip, with slightly thickened, warty walls; secretory trichomes also very abundant, some small with unicellular stalk and unicellular or bicellular head, others large, of laminaceous type, with unicellular stalk and spherical to ovoid head composed of 8 cells (*5*).

Powdered plant material

Greenish. Fragments of the leaf epidermis with sinuous walls; short, conical, unicellular covering trichomes with a finely striated cuticle; uniseriate, multicellular covering trichomes; 8-celled secretory trichomes of laminaceous type, others with unicellular to tricellular stalks and unicellular or, more rarely, bicellular heads; diacytic stomata, on the lower surface only (*1*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for rosmarinic, chlorogenic and caffeic acids (*1*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 2% total foreign matter and not more than 10% of stem fragments with a diameter greater than 1 mm (*1*).

Total ash

Not more than 12% (*1*).

Loss on drying

Not more than 10% (*1*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

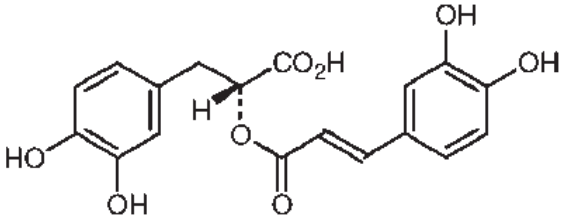
Chemical assays

Contains not less than 4.0% total hydroxycinnamic acids calculated as rosmarinic acid (*1*). Quantitative analysis is performed by spectrophotometry at 505 nm (*1*). Essential oil analysis is carried out according to the method described in the *European pharmacopoeia* (*1*).

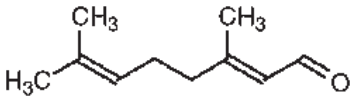
Major chemical constituents

The major characteristic constituents are the hydroxycinnamic acids (rosmarinic [up to 6%], *p*-coumaric, caffeic and chlorogenic acids), and an essential oil (0.02–0.37%) composed of more than 40% monoterpenes and more than 35% sesquiterpenes. The most significant terpenoid com-

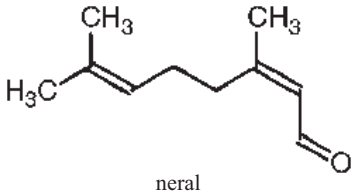
ponents are citral (a mixture of the isomers neral and geranial), citronellal, geraniol, nerol, linalool, farnesyl acetate, humulene (α-caryophyllene), β-caryophyllene and eremophilene. Other constituents include flavonoids, tannins and acidic triterpenes (e.g. ursolic and oleanolic acids) (*4, 6, 7, 13–15*). The structures of the major compound, rosmarinic acid, and terpenoid components are presented below.



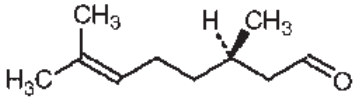
rosmarinic acid



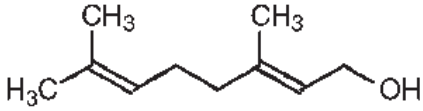
geranial



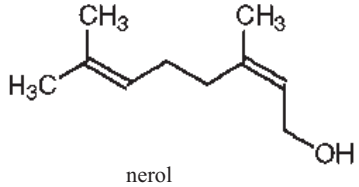
neral



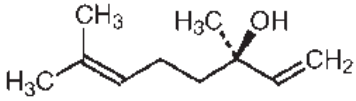
and enantiomer citronellal



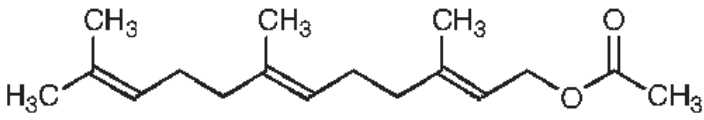
geraniol



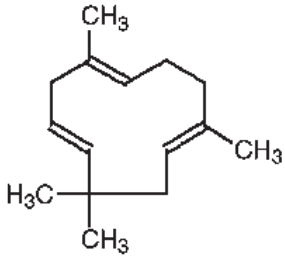
nerol



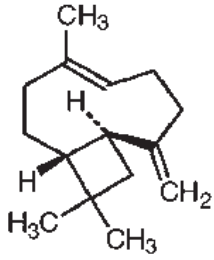
and enantiomer linalool



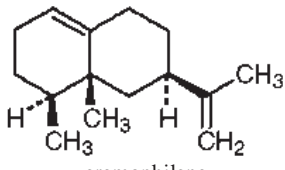
farnesyl acetate



humulene (α-caryophyllene)



β-caryophyllene



eremophilene

Medicinal uses

Uses supported by clinical data

Externally, for symptomatic treatment of herpes labialis (*16–18*).

Uses described in pharmacopoeias and in traditional systems of medicine

Orally as a carminative for gastrointestinal disorders, and as a sedative for treatment of nervous disturbances of sleep (*5*, *15*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of amenorrhoea, asthma, bee stings, coughs, dizziness, dysmenorrhoea, migraine headaches, tachycardia, toothache, tracheobronchitis and urinary incontinence (*6*, *19*).

Pharmacology

Experimental pharmacology

Antiviral activity

Aqueous extracts of Folium Melissae inhibited the replication in vitro of herpes simplex virus type 2, influenza virus A_2 (Mannheim 57) and vaccinia virus at a concentration of 10% (*20*). A dried aqueous extract of the leaves inhibited the replication of herpes simplex viruses in vitro at a concentration of 200 µg/ml (*18*). A condensed tannin isolated from an aque-

ous extract of the leaves inhibited haemagglutination induced by Newcastle disease virus or mumps virus; protected eggs and chick cell cultures from infection by Newcastle disease virus; and prevented haemagglutination by Newcastle disease, mumps and parainfluenza viruses 1, 2 and 3, but not by influenza viruses A and B (*21*). A tannin-free polyphenol fraction of an aqueous extract of the leaves was active against herpes simplex and vaccinia viruses in egg and cell culture systems (*22*). Aqueous extracts of the leaves have also been reported to have activity against Semliki Forest virus, influenza viruses and myxoviruses in vitro (*23*, *24*).

Antispasmodic activity

An ethanol extract of the leaves inhibited histamine- and barium-induced contractions of guinea-pig ileum in vitro (200 µg/ml), while an aqueous extract was inactive (*25*). A 30% ethanol extract did not inhibit acetylcholine- and histamine-induced contractions in guinea-pig ileum in vitro at concentrations up to 10 µl/ml (*26*). The essential oil inhibited contractions in guinea-pig ileum, rat duodenum and vas deferens, and rabbit jejunum and aorta in vitro (*27*, *28*). The essential oil also exhibited smooth muscle relaxant activity in guinea-pig tracheal muscle (ED_{50} 22 µg/ml) and in an electrically stimulated ileum myenteric plexus/longitudinal muscle preparation (ED_{50} 7.8 µg/ml) (*29*).

Behavioural effects

Inhalation of the essential oil had a weak tranquillizing effect in mice (*30*).

Clinical pharmacology

An open multicentre study of 115 patients with herpes simplex infections of the skin and transitional mucosa demonstrated that external applications of a 1% lyophilized aqueous extract of Folium Melissae in a cream base reduced the healing time of herpetic lesions from 10–14 days to 6–8 days (*18*). Treatment with the cream also prolonged the recidivation-free intervals, as compared with other topical virustatic preparations containing idoxuridine and tromantidine hydrochloride (*16*, *18*). A subsequent randomized, double-blind, placebo-controlled study of 116 patients with herpes simplex infections of the skin and transitional mucosa demonstrated a significant reduction in the size of herpetic lesions within 5 days in patients treated with the same cream ($P = 0.01$), as compared with placebo treatment (*17*, *18*).

Contraindications

External use: none. Internal use: see Precautions.

Warnings
No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility
A tincture of Folium Melissae was not mutagenic in vitro (*31*) and alcohol extracts had antimutagenic activity in vitro (*32*).

Pregnancy: teratogenic effects
Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

Pregnancy: non-teratogenic effects
Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

Nursing mothers
Internal use: no information available. Therefore, Folium Melissae should not be administered internally during lactation without medical supervision.

Paediatric use
Internal use: no information available. Therefore, Folium Melissae should not be administered internally to children without medical supervision.

Other precautions
No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions; pregnancy.

Adverse reactions
No information available.

Dosage forms
Comminuted crude drug; powder, tea bags, dried and fluidextracts for infusions and other galenical preparations (*7*, *14*, *15*). Store in a tightly closed container, protected from light (*1*). Do not store in plastic containers (*7*).

Posology

(Unless otherwise indicated)

Daily dosage for oral administration (for gastrointestinal disorders and as a sedative for nervous disturbances of sleep).

Infusion: 1.5–4.5 g crude drug per cup several times daily as needed (*15*); 45% alcohol extract (1:1): 2–4 ml three times daily (*5*); tincture (1:5 in 45% alcohol): 2–6 ml three times daily (*14*).

Daily dosage for topical application (for herpes labialis).

Cream containing 1% of a lyophilized aqueous extract applied 2–4 times daily from the appearance of prodromal signs to a few days after the healing of the lesions, for a maximum of 14 days (*14*, *18*).

References

1. *European pharmacopoeia*, 3rd ed., Suppl. 2000. Strasbourg, Council of Europe, 1999.
2. *Pharmacopoeia Hungarica*, 7th ed. Budapest, Hungarian Pharmacopoeia Commission, Medicina Kanyvkiado, 1986.
3. Bedevian AK. *Illustrated polyglottic dictionary of plant names in Latin, Arabic, Armenian, English, French, German, Italian and Turkish languages*. Cairo, Argus & Papazian Press, 1936.
4. Hänsel R et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Bd. 6: Drogen P–Z*, 5th ed. Berlin, Springer-Verlag, 1994.
5. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
6. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
7. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
8. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, PA, Blakiston, 1950.
9. Backer CA, Backhuisen van den Brink RC, eds. *Flora of Java. Vol. 2*. Noordhof, NVP, 1965.
10. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
11. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
12. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
13. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.

14. *ESCOP monographs on the medicinal use of plant drugs*. Fascicule 1. Elburg, European Scientific Cooperative on Phytotherapy, 1996.
15. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
16. Wölbling RH, Milbradt R. Klinik und Therapie des Herpes simplex. Der Allgemeinarzt. Vorstellung eines neuen phytotherapeutischen Wirkstoffes. *Therapiewoche*, 1984, 34:1193–1200.
17. Vogt HJ et al. Melissenextrakt bei Herpes simplex. *Allgemeinarzt*, 1991, 13:832–841.
18. Wölbling RH, Leonhardt K. Local therapy of herpes simplex with dried extract from *Melissa officinalis. Phytomedicine*, 1994, 1:25–31.
19. Boulos L. *Medicinal plants of North Africa*. Algonac, MI, Reference Publications Inc., 1983.
20. May G, Willuhn G. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. *Arzneimittel-Forschung*, 1978, 28:1–7.
21. Kucera LS, Herrmann EC. Antiviral substances in plants of the mint family (Labiatae). II. Tannin of *Melissa officinalis. Proceedings of the Society of Experimental Biology and Medicine*, 1967, 124:865–869.
22. Herrmann EC, Kucera LS. Antiviral substances in plants of the mint family (Labiatae). II. Nontannin polyphenol of *Melissa officinalis. Proceedings of the Society of Experimental Biology and Medicine*, 1967, 124:869–874.
23. Van den Berghe DA et al. Present status and prospects of plant products as antiviral agents. In: Vlietinck AJ, Dommisse RA, eds. *Advances in medicinal plant research*. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1985:47–99.
24. Konig B, Dustmann JH. The caffeoylics as a new family of natural compounds. *Naturwissenschaften*, 1985, 72:659–661.
25. Itokawa H et al. Studies on the constituents of crude drugs having inhibitory activity against contraction of the ileum caused by histamine or barium chloride. I. Screening test for the activity of commercially available crude drugs and the related plant materials. *Shoyakugaku Zasshi*, 1983, 37:223–228.
26. Forster HB, Niklas H, Lutz S. Antispasmodic effects of some medicinal plants. *Planta Medica*, 1980, 40:309–312.
27. Wagner H, Sprinkmeyer L. Über die pharmakologische Wirkung von Melissengeist. *Deutsche Apotheker Zeitung*, 1973, 113:1159–1166.
28. Debelmas AM, Rochat J. Étude pharmacologique des huiles essentielles. Activité antispasmodique etudiée sur une cinquantaine d'échantillons differents. *Plantes médicinales et Phytothérapie*, 1967, 1:23–27.
29. Reiter M, Brandt W. Relaxant effects on tracheal and ileal smooth muscles of the guinea-pig. *Arzneimittel-Forschung*, 1985, 35:408–414.
30. Buchbauer G et al. Fragrance compounds and essential oils with sedative effects upon inhalation. *Journal of Pharmaceutical Sciences*, 1993, 82:660–664.

31. Schimmer O et al. An evaluation of 55 commercial plant extracts in the Ames mutagenicity test. *Pharmazie*, 1994, 49:448–451.
32. Saigusa S et al. Antimutagenic activity of herbal extracts. II. Mechanism and DNA-repair enhancement. *Mutation Research*, 1982, 182:375.

Aetheroleum Menthae Piperitae*

Definition

Aetheroleum Menthae Piperitae is the essential oil obtained by steam distillation of the fresh overground parts of *Mentha* × *piperita* L. (Lamiaceae) (*1–4*).

Synonyms

Mentha piperita (L.) Huds., *M. piperita* Stokes, *M. balsamea* Willd. (*5*, *6*).

Selected vernacular names

Amentha, american mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nána, ni naa, ni'na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, piperita, pudeena, pum hub, yerba mota (*5–7*).

Geographical distribution

Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (*1*, *5*, *8*, *9*).

Description

A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petiolate, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (*5*, *8*, *10*).

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

Plant material of interest: essential oil

General appearance

A colourless, pale yellow or pale greenish-yellow liquid (*1*, *2*).

Organoleptic properties

Odour: characteristic, penetrating; taste: characteristic, pungent, followed by a sensation of cold (*1*, *2*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Thin-layer and gas chromatography for characteristic monoterpene profiles (*1*, *2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

Chemical

Acid value: not more than 1.4 (*1*, *2*).
Relative density: 0.900–0.916 (*1–3*).
Refractive index: 1.457–1.467 (*1–3*).
Optical rotation: –10° to –30° (*1–3*).
Solvent solubility: miscible with ethanol (96%), ether and methylene chloride (*1*, *2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*12*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

Radioactive residues

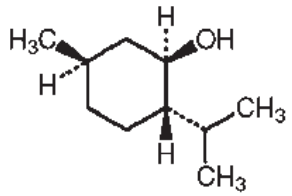
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

Chemical assays

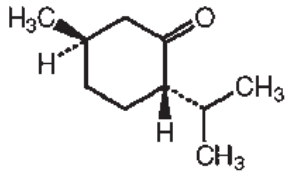
The monoterpene content determined by gas chromatography should be 1,8-cineole (6–14%), limonene (1–5%), menthone (14–32%), menthofuran (1–9%), isomenthone (2–10%), menthyl acetate (3–5%), menthol (30–55%), pulegone (not more than 4.0%) and carvone (not more than 1.0%). The ratio of 1,8-cineole to limonene should be greater than 2.0 (*1*, *2*).

Major chemical constituents

The major constituents are menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (*2*, *6*, *9*, *13*, *14*). The structures of the major monoterpenes, menthol and menthone, are presented below.



menthol



menthone

Medicinal uses

Uses supported by clinical data

Internally for symptomatic treatment of irritable bowel syndrome (*15–20*), and digestive disorders such as flatulence and gastritis (*21–23*). Externally for treatment of myalgia and headache (*21*, *24–27*).

Uses described in pharmacopoeias and in traditional systems of medicine

Internally and externally for the symptomatic treatment of catarrh and coughs (*21*, *22*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of dysentery, diabetes, dysmenorrhoea, fevers, jaundice and urinary infections (*7*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Aetheroleum Menthae Piperitae inhibited the growth in vitro of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Escherichia coli* (*28–30*), but did not affect the growth of *Bacillus cereus*, *Penicillium cyclopium* or *Aspergillus aegyptiacus* (*28*, *30*). The essential oil inhibited the growth in vitro of *Trichophyton equinum* and *T. rubrum* (at a concentration of 0.4 µg/ml) (*31*), *Aspergillus flavus*, *A. fumigatus* and *A. niger* (*32*).

Antispasmodic activity

The essential oil had smooth muscle relaxant activity in guinea-pig ileum (ED_{50} 26.0 mg/l) and trachea (ED_{50} 87.0 mg/l) in vitro (*33*), and inhibited electrically induced contractions of guinea-pig ileum (IC_{50} 0.176 mg/ml) in vitro (*34*). The essential oil decreased both the number and amplitude of spontaneous contractions, and inhibited spasms induced by barium chloride, pilocarpine and physostigmine in isolated segments of rabbit and cat ileum (inhibitory concentrations 0.05 µg/ml) (*35*). The essential oil (0.5 µmol/l) inhibited smooth muscle contractions of guinea-pig ileum in vitro induced by barium chloride, carbachol, histamine and potassium chloride (*36*). Both the essential oil and menthol act as calcium antagonists, since they inhibited the influx of calcium ions through smooth muscle of guinea-pig ileum and taenia coli isolated from humans (*36–39*). The essential oil and menthol inhibited smooth muscle contractions of guinea-pig ileum induced by potassium chloride (IC_{50} 28.1 and 21 µg/ml, respectively) and induced electrically (11.5 and 7.7 µg/ml, respectively) (*40*). Both also inhibited $^{45}Ca^{2+}$ uptake induced by potassium ion-dependent depolarization in brain synaptosomes and retinal neurons, and inhibited specific binding of [^{3}H]nitrendipine to ileal smooth muscle, synaptosomes and retinal neurons (*40*). The essential oil relaxed carbachol-contracted guinea-pig taenia coli (IC_{50} 22.1 µg/ml), and inhibited spontaneous contractions in isolated guinea-pig colon (IC_{50} 25.9 µg/ml) and rabbit jejunum (IC_{50} 15.2 µg/ml) (*41*). The essential oil also attenuated contractile responses in guinea-pig taenia coli induced by acetylcholine, histamine, serotonin (5-hydroxytryptamine)

and substance P (*41*). Contraction of Oddi's sphincter induced by morphine was reversed after intravenous administration of the essential oil to guinea-pigs (1.0 mg/kg body weight). However, intravenous injection of the essential oil to guinea-pigs (25 mg/kg body weight) was found to increase spasms of the sphincter (*42*). Intragastric administration of the essential oil exhibited cholagogic activity in rats. This activity was attributed to (–)-menthol, a major constituent of the essential oil (*43*).

Antifoaming activity

The essential oil (0.1%) had antifoaming and carminative activity in vitro; however, the antifoaming effect was less than that observed with a combination of dimethicone and silica (*44*).

Toxicology

Intragastric administration of the essential oil (100 mg/kg body weight) to rats daily for 28 days induced histopathological changes (scattered cyst-like spaces) in the white matter of the cerebellum. No behavioural or clinical symptoms due to the encephalopathy were observed (*45*).

Clinical pharmacology

Antispasmodic activity

Irritable bowel syndrome

Aetheroleum Menthae Piperitae is a carminative with antispasmodic activity that reduces intracolonic pressure (*22*). In an open study of 20 patients, an aqueous suspension of peppermint oil (British Pharmacopoeia Standard) injected along the biopsy channel of a colonoscope relieved colonic spasms within 30 seconds, allowing easier passage of the instrument or facilitating polypectomy (*16*). The essential oil relaxed the oesophageal sphincter when administered orally (15 drops [about 0.88 ml] oil in 30 ml water), decreasing the pressure differential between the stomach and oesophagus, and allowing reflux to occur (*46*).

In a double-blind, placebo-controlled, crossover clinical trial, 18 patients with symptoms of irritable bowel syndrome were treated daily with three enteric-coated gelatin capsules, each containing either 0.2 ml essential oil or a placebo for 3 weeks. Patients reported feeling significantly better while taking capsules containing the essential oil than when taking those containing placebo ($P < 0.01$) and considered the essential oil significantly better than the placebo in relieving abdominal symptoms ($P < 0.005$) (*19*). These results were confirmed in a later study (*15*). A matched-pair, placebo-controlled trial assessed the efficacy of the essential oil in the treatment of 40 patients with symptoms of irritable bowel syndrome. After

14 days of treatment with 1–2 enteric-coated gelatin capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed an increase in intestinal transit time, and subjective improvement in the feeling of fullness, bloating, bowel noises and abdominal pain, as compared with patients who received the placebo (*20*).

Administration of the essential oil to patients undergoing barium enemas relieved the associated colonic spasms (*47*, *48*). However, two earlier trials failed to confirm the antispasmodic and analgesic activity of the essential oil in the treatment of irritable bowel syndrome (*49*, *50*). A double-blind, placebo-controlled trial assessed the effects of peppermint oil in 34 patients with symptoms of irritable bowel syndrome. After 4 weeks of treatment with two capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed no significant difference in their overall symptoms, as compared with those who received the placebo treatment (*49*).

A prospective, randomized double-blind, placebo-controlled trial assessed the efficacy and safety of enteric-coated capsules containing 0.2 ml essential oil (one capsule 3–4 times daily for 1 month) for the symptomatic treatment of 110 patients with irritable bowel syndrome. After treatment, 79% of patients in the treatment group and 43% of those in the placebo group experienced alleviation of severe abdominal pain; 83% of the treated group and 32% of the placebo group had reduced abdominal distention and a reduced stool frequency; 73% of the treated group and 31% of the placebo group had fewer bowel noises; and 79% of the treated group and 22% of the placebo group had less flatulence (*17*).

A review of five randomized, double-blind, placebo-controlled clinical trials assessed the efficacy of the essential oil in the symptomatic treatment of irritable bowel syndrome (*18*). By measuring the improvement of symptoms, the meta-analysis showed that two of the trials (*49*, *51*) did not show a significant difference between the essential oil and the placebo. However, three of the trials demonstrated significant improvements in symptoms after treatment with the essential oil (*15*, *19*, *52*). Although there were methodological flaws in most of the trials analysed, the analysis suggested that there was a significant positive effect of the essential oil ($P < 0.001$) on the symptomatic treatment of irritable bowel syndrome, as compared with the placebo (*18*).

Dyspepsia

A double-blind, placebo-controlled multicentre study involving 45 patients with non-ulcer dyspepsia assessed the change in pain intensity and Clinical Global Impression Scale after treatment with an enteric-coated

capsule containing a combination of the essential oil (90 mg) and caraway oil (50 mg). After 4 weeks of treatment with the essential oil/caraway oil capsules (one capsule three times daily), 63% of patients were free of pain; 89.5% had less pain; and 94.5% showed improvements in the Clinical Global Impression Scale (*23*). In another study, oral administration of the essential oil (0.2 ml) delayed the gastric emptying time in healthy volunteers and in patients with dyspepsia (*53*).

Analgesic activity

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a combination product of the essential oil (peppermint oil) and Aetheroleum Eucalypti (eucalyptus oil) for headache relief in 32 patients. Five different preparations were used (all in 90% ethanol, to a final weight of 100 g): 10 g peppermint oil and 5 g eucalyptus oil; 10 g peppermint oil and traces of eucalyptus oil; traces of peppermint oil and 5 g eucalyptus oil; and traces of both peppermint oil and eucalyptus oil; or a placebo. The test preparations or placebo were applied topically to large areas of the forehead and temples, and the effects on neurophysiological, psychological and experimental algesimetric parameters were measured. The preparations improved cognitive performance, and induced muscle relaxation and mental relaxation, but had no effect on sensitivity to headache (*27*). A randomized, double-blind, placebo-controlled study assessed the efficacy of the essential oil in the treatment of 41 patients suffering from chronic tension headache. At each headache episode, patients were treated orally with two capsules of either paracetamol (1 g) or placebo, or external application of 10% essential oil in ethanol, or a placebo solution. Compared with the placebo solution, the 10% essential oil preparation produced a significant ($P < 0.05$) reduction in headache intensity within 15 minutes. Paracetamol was also more effective than the oral placebo but did not differ significantly from topical treatment with the essential oil (*54*).

Contraindications

Preparations of Aetheroleum Menthae Piperitae should not be used internally by patients with inflammation of the gastrointestinal tract or gall bladder, or with impaired liver function (*21*). Hypersensitivity to the essential oil has been reported (*55–57*).

Warnings

Aetheroleum Menthae Piperitae preparations should not be applied to the face, especially the nose, of infants or young children (*21*, *22*). Keep out of reach of children.

Precautions

General

Patients with achlorhydria (due to medication with histamine H_2 receptor antagonists) should only use enteric-coated preparations (*19*, *58*).

Carcinogenesis, mutagenesis, impairment of fertility

Aetheroleum Menthae Piperitae was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA1535 (*59*).

Paediatric use

No information available. Therefore, Aetheroleum Menthae Piperitae should not be administered to children without medical supervision. (See also Contraindications and Warnings.)

Other precautions

No information available on precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; or nursing mothers. Therefore, Aetheroleum Menthae Piperitae should not be administered during pregnancy or lactation without medical supervision.

Adverse reactions

Following internal administration of Aetheroleum Menthae Piperitae, gastric complaints have been reported in individuals sensitive to the essential oil (*21*). The use of non-enteric-coated essential oil preparations has occasionally caused heartburn, especially in patients suffering from reflux oesophagitis (*58*). Skin rashes, headache, heartburn, perianal burning, bradycardia, muscle tremors and ataxia have been reported as rare side-effects, usually associated with overdose (*18*, *56*, *60–65*). Recurrent muscle pain has been associated with the ingestion of the essential oil (*66*). Following external administration of Aetheroleum Menthae Piperitae, skin irritation has been reported (*58*).

Dosage forms

Essential oil, concentrated peppermint emulsion, peppermint spirit and other galenic preparations (*1*, *21*). Store in a well-closed container, protected from light (*1*, *2*).

Posology

(Unless otherwise indicated)

Internal use

For digestive disorders, daily dosage: 0.2–0.4 ml essential oil three times daily in dilute preparations (*58*, *67*) or suspensions (*19*). By inhalation: 3–4 drops essential oil in hot water (*21*). Lozenges: 2–10 mg essential oil per lozenge (*58*).

For irritable bowel syndrome, daily dosage: 0.2–0.4 ml essential oil three times daily in enteric-coated capsules (*21*, *58*).

External use

5–20% essential oil in dilute, semisolid or oily preparations; 5–10% essential oil in aqueous-ethanol; nasal ointments containing 1–5% crude drug (*21*).

References

1. *British pharmacopoeia*. *Vol. I* (International edition and addendum). London, Her Majesty's Stationery Office, 1995.
2. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
3. *Farmakope Indonesia Edisi Ketiga*. Jakarta, Departemen Kesehatan, Republik Indonesia, 1979.
4. *Pharmacopoeia Hungarica*, 7th ed. Budapest, Hungarian Pharmacopoeia Commission, Medicina Konyvkiado, 1986.
5. *African pharmacopoeia*. *Vol. 1*, 1st ed. Lagos, Organization of African Unity, Scientific Technical & Research Commission, 1985.
6. Blaschek W et al., eds. *Hagers Handbuch der pharmazeutischen Praxis*. *Folgeband 2: Drogen A–K*, 5th ed. Berlin, Springer-Verlag, 1998.
7. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
8. Youngken HW. *Textbook of pharmacognosy.* Philadelphia, PA, Blakiston, 1950.
9. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
10. Evans WC. *Pharmacognosy*, 14th ed. London, WB Saunders Co., 1996.
11. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
12. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
13. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
14. Samuelsson G. *Drugs of natural origin, a textbook of pharmacognosy.* Stockholm, Swedish Pharmaceutical Press, 1992.

15. Dew MJ, Evans BK, Rhodes J. Peppermint oil for the irritable bowel syndrome: a multicentre trial. *British Journal of Clinical Practice*, 1984, 38:394, 398.
16. Leicester RJ, Hunt RH. Peppermint oil to reduce colonic spasm during endoscopy. *Lancet*, 1982, 2:989.
17. Liu JH et al. Peppermint oil and irritable bowel syndrome. *Journal of Gastroenterology*, 1997, 32:765–768.
18. Pittler MH, Ernest E. Peppermint oil for irritable bowel syndrome: a critical review and meta-analysis. *American Journal of Gastroenterology*, 1998, 93:1131–1135.
19. Rees WDW, Evans BK, Rhodes J. Treating irritable bowel syndrome with peppermint oil. *British Medical Journal*, 1979, 280:835–836.
20. Wildgrube HJ. Untersuchungen zur Wirksamkeit von Pfefferminzöl auf Beschwerdebild und funktionelle Parameter bei Patienten mit Reizdarm-Syndrom (Studie). *Naturheilpraxis*, 1988, 41:591–596.
21. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
22. Reynolds JEF, ed. *Martindale, the extra pharmacopoeia*, 30th ed. London, Pharmaceutical Press, 1996.
23. May B et al. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. *Arzneimittel-Forschung*, 1996, 46:1149–1153.
24. Bromm B et al. Effects of menthol and cold on histamine-induced itch and skin reactions in man. *Neuroscience Letters*, 1995, 187:157–160.
25. Göbel H et al. Effect of peppermint and eucalyptus oil preparations on neurophysiological and experimental algesimetric headache parameters. *Cephalalgia*, 1994, 14:228–234.
26. Göbel H, Schmidt G. Effekt von Pfefferminz- und Eukalyptusölpräparationen in experimentellen Kopfschmerzmodellen. *Zeitschrift für Phytotherapie*, 1995, 16:23–33.
27. Göbel H et al. Essential plant oils and headache mechanisms. *Phytomedicine*, 1995, 2:93–102.
28. El-Keltawi NEM et al. Antimicrobial activity of some Egyptian aromatic plants. *Herba Polonica*, 1980, 26:245–250.
29. Janssen AM et al. Screening for antibacterial activity of some essential oils by the agar overlay technique. *Pharmaceutisch Weekblad (Scientific Edition)*, 1986, 8:289–292.
30. Ross SA et al. Antimicrobial activity of some Egyptian plants. *Fitoterapia*, 1980, 51:201–205.
31. Begum J et al. Studies on essential oils for their antibacterial and antifungal properties. Part I. Preliminary screening of 35 essential oils. *Bangladesh Journal of Science and Industry Research*, 1993, 28:25–34.
32. Leifertova I, Lisa M. The antifungal properties of higher plants affecting some species of the genus *Aspergillus*. *Folia Pharmacie (Prague)*, 1979, 2:29–54.

33. Reiter M, Brandt W. Relaxant effects on tracheal and ileal smooth muscles of the guinea-pig. *Arzneimittel-Forschung*, 1985, 35:408–414.
34. Taddei I et al. Spasmolytic activity of peppermint, sage and rosemary essences and their major constituents. *Fitoterapia*, 1988, 59:463–468.
35. Gunn JWC. The carminative action of volatile oils. *Journal of Pharmacology and Experimental Therapeutics*, 1920, 16:93–143.
36. Taylor BA, Duthie HL, Luscombe DK. Inhibitory effect of peppermint oil on gastrointestinal smooth muscle. *Gut*, 1983, 24:A992.
37. Taylor BA, Duthie HL, Luscombe DK. Inhibitory effect of peppermint and menthol on human isolated coli. *Gut*, 1984, 25:A1168–A1169.
38. Taylor BA, Duthie HL, Luscombe DK. Calcium antagonist activity of menthol on smooth gastrointestinal muscle. *British Journal of Clinical Pharmacology*, 1985, 20:293P–294P.
39. Taylor BA et al. Mechanism by which peppermint oil exerts its relaxant effect on gastrointestinal smooth muscle. *Journal of Pharmacy and Pharmacology*, 1985, 37 (Suppl. 1):104.
40. Triggle DJ et al. Peppermint oil as a calcium channel antagonist in intestinal smooth muscle and neuronal preparations. *Gastroenterology*, 1988, 94:A465.
41. Hills JM, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea-pigs. *Gastroenterology*, 1991, 101:55–65.
42. Giachetti D, Taddei E, Taddei I. Pharmacological activity of essential oils on Oddi's sphincter. *Planta Medica*, 1988, 54:389–392.
43. Yamahara J et al. Cholagogic substances in Menthae Herba. *Japanese Journal of Pharmacology*, 1985, 39:280.
44. Harries N, James KC, Pugh WK. Antifoaming and carminative actions of volatile oils. *Journal of Clinical Pharmacy*, 1978, 2:171–177.
45. Thorup I et al. Short-term toxicity in rats dosed with peppermint oil. *Toxicology Letters*, 1983, 19:207–210.
46. Sigmund CJ, McNally EF. The action of a carminative on the lower esophageal sphincter. *Gastroenterology*, 1969, 56:13–18.
47. Kingham JGC. Peppermint oil and colonic spasm. *Lancet*, 1995, 346:986.
48. Sparks MJW et al. Does peppermint oil relieve spasm during barium enema? *British Journal of Radiology*, 1995, 68:841–843.
49. Nash P et al. Peppermint oil does not relieve the pain of irritable bowel syndrome. *British Journal of Clinical Practice*, 1986, 40:292–293.
50. Rogers J, Tay HH, Misiewicz JJ. Peppermint oil. *Lancet*, 1988, ii:98–99.
51. Carling L, Svedberg L-E, Hulten S. Short-term treatment of the irritable bowel syndrome: a placebo-controlled trial of peppermint oil against hyoscyamine. *Opuscula Medica*, 1989, 34:55–57.
52. Lech AY et al. Behandling af colon irritabile med pebermynteolie. *Ugeskrift for Laeger*, 1988, 150:2388–2389.

53. Dalvi SS et al. Effect of peppermint oil on gastric emptying in man: a preliminary study using a radiolabelled solid test meal. *Indian Journal of Physiology and Pharmacology*, 1991, 35:212–214.
54. Göbel H et al. Oleum menthae piperitae: Wirkmechanismen und klinische Effektivität bei Kopfschmerz vom Spannungstyp. In: Loew D, Rietbrock N, eds. *Phytopharmaka in Forschung und klinischer Anwendung*. Darmstadt, Steinkopff Verlag, 1995:817–824.
55. Dooms-Goossens A et al. Turpentine-induced hypersensitivity to peppermint oil. *Contact Dermatitis*, 1977, 3:304–308.
56. Fisher A. Reactions to menthol. *Cutis*, 1986, 38:17–18.
57. Saito F, Oka K. Allergic contact dermatitis due to peppermint oil. *Skin Research*, 1990, 32 (Suppl. 9):161–167.
58. *ESCOP monographs on the medicinal uses of plant drugs.* Fascicule 3. Devon, European Scientific Cooperative on Phytotherapy, 1997.
59. Andersen PH, Jensen NJ. Mutagenic investigation of peppermint oil in the *Salmonella*/mammalian microsome test. *Mutation Research*, 1984, 138:17–20.
60. Mintec capsules. *Pharmaceutical Journal*, 1986, 237:355.
61. Burr ML et al. Food allergic asthma in general practice. *Human Nutrition and Applied Nutrition*, 1985, 39A:349–355.
62. Lubow RM et al. Plasma-cell gingivitis: report of a case. *Journal of Periodontology*, 1984, 55:235–241.
63. Luke E. Addiction to mentholated cigarettes. *Lancet*, 1962, i:110.
64. Moller NE et al. Allergic and pseudo-allergic reactions caused by penicillins, cocoa and peppermint additives in penicillin factory workers examined by basophil histamine release. *Acta Pharmacologia Toxicologia*, 1984, 55:139–144.
65. Parys BT. Chemical burns resulting from contact with peppermint oil. *Burns including Thermal Injuries*, 1983, 9:374–375.
66. Williams B. Palindromic rheumatism. *Medical Journal of Australia*, 1972, 2:390.
67. Hänsel R. *Phytopharmaka*, 2nd ed. Berlin, Springer-Verlag, 1991.

Folium Menthae Piperitae*

Definition
Folium Menthae Piperitae consists of the dried leaves of *Mentha* × *piperita* L. (Lamiaceae) (*1*–*3*).

Synonyms
Mentha piperita (L.) Huds., *M. piperita* Stokes, *M. balsamea* Willd. (*1*, *4*).

Selected vernacular names
Amentha, American mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nána, ni naa, ni'na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, piperita, pudeena, pum hub, yerba mota (*1*, *4*, *5*).

Geographical distribution
Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (*1*, *3*, *6*, *7*).

Description
A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petiolate, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (*1*, *7*, *8*).

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

Plant material of interest: dried leaves

General appearance

Green to greenish-brown. Leaves whole, broken or cut; thin, fragile; whole leaf 3–9 cm long and 1–3 cm wide, often crumpled. Lamina oval or lanceolate; apex acuminate; margin sharply dentate; base asymmetrical. Venation pinnate, prominent on the lower surface, with lateral veins leaving the midrib at an angle of about 45°. Lower surface slightly pubescent and secretory trichomes visible under a hand lens as bright yellowish points. Petiole grooved, usually up to 1 mm in diameter and up to 1 cm long (*2*).

Organoleptic properties

Odour: characteristic, penetrating; taste: characteristic, aromatic (*2*).

Microscopic characteristics

Upper epidermis composed of large, clear epidermal cells with sinuous, vertical walls and possessing few or no stomata, few glandular trichomes present; palisade parenchyma, comprising a layer of columnar cells rich in chloroplasts; spongy parenchyma, of 4–6 layers of irregularly shaped chloroplastid-containing cells and intercellular air-spaces. Lower epidermis of small epidermal cells with sinuous, vertical walls and numerous diacytic stomata; in the region of veins and midrib, exhibits non-glandular and glandular trichomes as outgrowths; non-glandular trichomes uniseriate, papillose, 1–8-celled; glandular trichomes have 1–2-celled stalk and 1–8-celled glandular head containing the essential oil. Calcium oxalate crystals absent; pollen grains spheroidal and smooth (*1*, *4*, *7*, *8*).

Powdered plant material

Brownish-green. Fragments of leaf tissue with cells of epidermis having sinuous walls, cuticle striated over the veins, diacytic stomata present predominantly on the lower epidermis; epidermis fragments from near leaf margin with isodiametric cells showing distinct beading and pitting in anticlinal walls; covering trichomes short, conical, unicellular, bicellular or elongated, uniseriate multicellular (3–8 cells) with striated cuticle. Glandular trichomes of 2 types: either with unicellular base with small, rounded, unicellular head 15–25 µm in diameter; or with unicellular base with enlarged, oval multicellular head 55–70 µm in diameter composed of 8 radiating cells; dorsoventral mesophyll fragments with a single palisade layer and 4–6 layers of spongy parenchyma; yellowish crystals of menthol under the cuticle of secretory cells. Calcium oxalate crystals absent (*1*, *2*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography (*1*, *2*). Gas chromatography of the steam-distilled essential oil (*9*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 5% stems, the diameter of which must be not more than 1.5 mm; not more than 8% leaves showing brown stains due to *Puccinia menthae* (*2*); not more than 2% other foreign matter (*2*).

Total ash

Not more than 15% according to the *European pharmacopoeia* (*2*); not more than 12% according to the *African pharmacopoeia* (*1*).

Acid-insoluble ash

Not more than 1.5% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*11*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Sulfated ash, water-soluble extractive, alcohol-soluble extractive, and loss on drying tests to be established in accordance with national requirements.

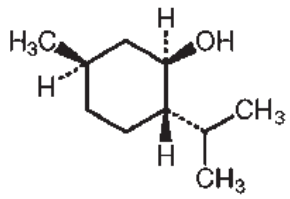
Chemical assays

Whole and cut leaves contain not less than 1.2% and 0.9% (v/w) essential oil, respectively, determined as described in the *European pharmacopoeia* (*2*).

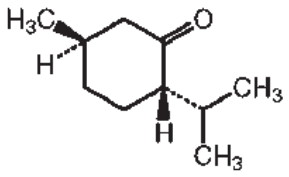
Major chemical constituents

The major constituent of the leaves is the essential oil (0.5–4%), which contains menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (*2*, *4*, *6*, *12*, *13*).

The structures of the major monoterpenes, menthol and menthone, are presented below.



menthol



menthone

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Symptomatic treatment of dyspepsia, flatulence and intestinal colic (*1*, *3*, *14*, *15*).

Uses described in folk medicine, not supported by experimental or clinical data

As an emmenagogue, vermifuge, lactation enhancer and sedative. Also used to treat bronchitis, bacillary dysentery, diabetes, diarrhoea, dysmenorrhoea, fevers, hypertension, jaundice, nausea, pain, and respiratory and urinary tract infections (*5*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Extracts of Folium Menthae Piperitae have antibacterial and antiviral activity in vitro. Addition of ground leaves to the agar medium inhibited the growth of *Salmonella typhimurium*, *Staphylococcus aureus* and *Vibrio parahaemolyticus* at concentrations of 0.1–2.0% (w/v) (*16*). Aqueous and ethanol extracts of the leaves reduced the number of plaques of the rinderpest virus at concentrations of 4–8 mg/ml (*17*). Aqueous extracts of the leaves demonstrated activity against the following viruses in egg and cell culture: Newcastle disease, herpes simplex, vaccinia, Semliki Forest and West Nile (*18*).

Smooth muscle contraction

A 31% ethanol extract of the leaves inhibited both acetylcholine- and histamine-induced smooth muscle contractions in guinea-pig ileum in vitro at a concentration of 10 ml/l (*19*, *20*). The results were similar to those obtained with 0.13 mg atropine (*19*). An aqueous flavonoid fraction isolated from a leaf extract inhibited barium chloride-induced muscle contractions of guinea-pig ileum in vitro at a concentration corresponding to 0.5 g leaves/ml (*21*).

Choleretic activity

Injection of a leaf infusion (0.5 ml) or a flavonoid fraction (equivalent to 3.3 g leaves/kg body weight) increased the amount of bile acids in cannulated rats and dogs (dose 0.4 mg/kg body weight) (*21*, *22*). A mixture of flavonoids, isolated from the leaves, had choleretic activity in dogs (2 mg/kg body weight) (*23*). Flavomentin, a flavonoid isolated from the leaves, stimulated bile secretion and the synthesis of bile acids in dogs (2 mg/kg body weight) (*24*). Intragastric administration of a 30% ethanol extract of the leaves to rats (1 ml/kg body weight) increased bile flow by 43%. The extract did not induce sedation in mice at doses up to 10 ml/kg body weight (*20*).

Anti-oedema activity

Topical application of a methanol leaf extract to mice (2.0 mg/ear) inhibited ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate (*25*).

Analgesic activity

Intragastric administration of a 30% ethanol extract of the leaves inhibited phenylbenzoquinone-induced writhing in mice (ED_{50} 2.1 ml/kg body weight) (*20*).

Toxicology
Intragastric administration of a leaf extract (50 g leaves infused with 500 ml hot water for 10 minutes, then spray-dried) to 12 mice (4 g/kg body weight as a single dose) did not result in central nervous system depression, toxic effects or mortality (*26*).

Clinical pharmacology
None.

Contraindications
No information available.

Warnings
No information available.

Precautions

General
Patients with gallstones should not use Folium Menthae Piperitae unless under medical supervision (*15*).

Other precautions
No information available on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Folium Menthae Piperitae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions
No information available.

Dosage forms
Dried leaves (*2*, *3*). Tincture and infusions (*6*). Store in a well-closed container, protected from light (*2*).

Posology
(Unless otherwise indicated)
Daily dosage: 1–3 g crude drug three times daily (*14*, *27*). Infusion: pour 150 ml hot water over 1.5–3.0 g (one tablespoon) dried leaves, steep for

10 minutes, strain and drink three times daily between meals (*6*, *15*, *28*). Tincture: 2–3 ml (1:5, 45% ethanol) three times daily (*14*).

References

1. *African pharmacopoeia*. *Vol. 1*, 1st ed. Lagos, Organization of African Unity, Scientific Technical & Research Commission, 1985.
2. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
3. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
4. Blaschek W et al., eds. *Hagers Handbuch der pharmazeutischen Praxis*. *Folgeband 2: Drogen A–K*, 5th ed. Berlin, Springer-Verlag, 1998.
5. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
6. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
7. Youngken HW. *Textbook of pharmacognosy,* 6th ed. Philadelphia, PA, Blakiston, 1950.
8. Evans WC. *Pharmacognosy*, 14th ed. London, WB Saunders Co., 1996.
9. *Pharmacopoeia Hungarica*, 7th ed. Budapest, Hungarian Pharmacopoeia Commission, Medicina Konyvkiado, 1986.
10. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
11. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
12. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
13. Samuelsson G. *Drugs of natural origin, a textbook of pharmacognosy.* Stockholm, Swedish Pharmaceutical Press, 1992.
14. Bradley PR, ed. *British herbal compendium*. *Vol. 1*. Bournemouth, British Herbal Medicine Association, 1992.
15. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
16. Aktug SE, Karapinar M. Sensitivity of some common food-poisoning bacteria to thyme, mint and bay leaves. *International Journal of Food Microbiology*, 1986, 3:349–354.
17. Alwan AH et al. Antiviral activity of some Iraqi indigenous plants. *International Journal of Crude Drug Research*, 1988, 2:107–111.
18. Herrmann EC Jr, Kucera LS. Antiviral substances in plants of the mint family (Labiatae). III. Peppermint (*Mentha piperita*) and other mint plants. *Proceedings of the Society for Experimental Biology and Medicine*, 1967: 874–878.

19. Forster HB et al. Antispasmodic effects of some medicinal plants. *Planta Medica*, 1980, 40:309–319.
20. Leslie GB. A pharmacometric evaluation of nine Bio-Strath herbal remedies. *Medita*, 1978, 8:3–19.
21. Lallement-Guilbert N, Bézanger-Beauquesne L. Recherches sur les flavonoides quelques Labiees médicinales (romarin, menthe poivrée, suage officinale). *Plantes médicinales et Phytothérapie*, 1970, 4:92–107.
22. Steinmetzer K. Experimentelle Untersuchungen über Cholagoga. *Wiener Klinische Wochenschrift*, 1926, 39:1418–1422, 1455–1457.
23. Pasechnik IK. Study of choleretic properties specific to flavonoids from *Mentha piperita* leaves. *Farmakologiia Toksikologiia*, 1966, 21:735–737.
24. Pasechnik IK, Gella EV. Choleretic preparation from peppermint. *Farmatsevtychnyi Zhurnal (Kiev)*, 1966, 21:49–53.
25. Yasukawa K et al. Inhibitory effect of edible plant extracts on 12-*O*-tetradecanoylphorbol-13-acetate-induced ear edema in mice. *Phytotherapy Research*, 1993, 7:185–189.
26. Della Loggia R et al. Evaluation of some pharmacological activities of a peppermint extract. *Fitoterapia*, 1990, 61:215–221.
27. Wichtl M. Pfefferminzblätter. In: Wichtl M, ed. *Teedrogen*, 2nd ed. Stuttgart, Wissenschaftliche Verlägsgesellschaft, 1989:372–374.
28. *ESCOP monographs on the medicinal uses of plant drugs*. Fascicule 3. Devon, European Scientific Cooperative on Phytotherapy, 1997.

Herba Millefolii

Definition

Herba Millefolii consists of the whole or cut, dried flowering tops (*1*, *2*) or aerial parts collected during the flowering season (*3*, *4*) of *Achillea millefolium* L. (Asteraceae).

Synonyms

Achillea borealis Bong., *A. lanulosa* Nutt., *A. magna* auct., *A. millefolium* ssp. *borealis* (Bong.) Breitung., *A. millefolium* ssp. lanulosa (Nutt.) Piper, *A. millefolium* var. *occidentale* DC (*5*).

Selected vernacular names

Achillée, achillenkraut, amelotu, artemisia bastarda, Bauchwehkraut, berbe militaris, biranjasif, bloodwort, bumadaran, carpenter's grass, carpenter's weed, chipmunk grass, centofoglie, cickafark, ciento en rama, common yarrow, daun seribu, dog daisy, egel tologch ovs, erba da carpentierir, erba da falegnam, erva d'o marchese, flor de la pluma, gandana, gordoloba, green arrow, herbe au charpentier, herbe de millefeuille, hezarbarg, Jungfraukraut, Katzenkraut, knight's milfoil, mil de tama, mil en rama, mil flores, mil hojas, milefolio, milfoil, millefolium, milenrama, nosebleed, old man's pepper, oum alf ouraka, pharange, saigum, sanguinary, sataraatyoutas, Schafgarbe, Schafgarbenkraut, seiyonokogiriso, seiyounokogirisou, sneezeweed, soldier's milfoil, stratictes, tansy, thou alf ouraka, thousand leaf, thousand leaf grass, thousand seal, thousand weed, trava tysyachelistnik, troneto, umm alf waraqah, western yarrow, wound wort, yarrow, yerba de carpintero, yerba de la muela (*2*, *6*–*10*).

Geographical distribution

Native to Asia, Europe and North America, now widely distributed and cultivated in the temperate regions of the world (*2*, *7*, *8*, *11*, *12*).

Description

A perennial herb, 30–90 cm in height, with aromatic odour and greyish-green colour from the numerous small hairs; stem angular. Leaves green or

greyish-green, faintly pubescent on the upper surface and more pubescent on the lower surface, 2–3 pinnately divided with linear lobes and a finely pointed whitish tip, alternate, clustered at the base of the stem. Flowering heads (capitula) in a flat-topped corymb (3–5 cm in diameter), small, pedunculate, varying in colour from white to pink, magenta and red; involucral bracts in few rows, the outer somewhat shorter than the inner, with a scarious margin. Outer florets in each capitulum usually 5, female, ligulate with more or less 3-dentate, patent ligules; inner florets hermaphrodite, 5-lobed, with compressed corolla tube and a receptacle scale at the base. Fruit a compressed achene, oblong or obovate, without pappus (*1*).

Plant material of interest: dried flowering tops and aerial part

General appearance

Flowering tops: Leaves green or greyish-green, faintly pubescent on the upper surface and more pubescent on the lower surface, 2–3 pinnately divided with linear lobes and a finely pointed whitish tip. The capitula are arranged in a corymb at the end of the stem. Each capitulum (3–5 cm in diameter) consists of the receptacle, usually 4 or 5 ligulate ray-florets and 3–20 tubular disc florets. The involucre consists of 3 rows of imbricate lanceolate, pubescent green bracts arranged with a brownish or whitish, membranous margin. The receptacle is slightly convex, and in the axillae of paleae, bears a ligulate ray floret with a 3-lobed, whitish or reddish ligule and tubular disc florets with a radial, 5-lobed, yellowish or light brownish corolla. The pubescent green, partly brown or violet stems are longitudinally furrowed, up to 3 mm thick with a light-coloured medulla (*1*).

Aerial part: Stems rounded, pubescent, furrowed, usually unbranched, 40 cm or more in length, distinctly woolly, pale green, sometimes purplish. Lanceolate leaves, up to 15 cm in length and 3 cm in width, 2 to 3 pinnate with the ultimate segments linear and subulate, pale greyish-green and covered with long white hairs; lower leaves with a short petiole, upper leaves sessile, often with two or three small axillary leaves at the base. Flowers numerous, in dense terminal corymbs, each capitulum about 3–5 cm in diameter with an ovoid involucre composed of 3 rows of imbricate lanceolate, pubescent green bracts arranged with a brownish or whitish, membranous margin; 4 or 5 white, pink or reddish ligulate ray-florets and 3–20 white or cream tubular disc florets; achenes 2 mm long, shiny, greyish-brown, slightly curved (*1*, *3*, *4*).

Organoleptic properties

Odour: slightly aromatic; taste: bitter, faintly aromatic (*3*, *4*, *7*).

Microscopic characteristics

Aerial part: Stem shows epidermal cells axially elongated with occasional anomocytic stomata and a faintly striated cuticle; abundant covering and scattered glandular trichomes; cortex narrow, parenchymatous with several layers of collenchyma in the ridges; numerous vascular bundles, arranged in a ring in transverse section, each with a small group of phloem and a wide cap of thick-walled, lignified pericyclic fibres; parenchymatous cells of outer pith lignified and pitted, those of the central region unlignified and sometimes collapsed in older stems forming a hollow. Leaf cells isobilateral, with palisades composed of 1–3 layers; upper and lower epidermal cells with sinuous anticlinal walls and numerous anomocytic stomata; abundant covering trichomes and scattered glandular trichomes occurring on both epidermises. Flower epidermal cells consisting of bracts, longitudinally elongated, thin-walled, filled with dark brown striated pigment, scattered covering trichomes and occasional stomata; the inner central region composed of elongated cells with lignified and finely pitted walls. Corolla of the ray floret with the epidermis of the ligule composed of wavy-walled cells with rounded papillae; corolla of the disc floret composed of rectangular cells with moderately thickened walls; numerous small cluster crystals of calcium oxalate occur in both ray and disc florets. Pollen grains spherical, 30–35 µm in diameter, with a spiny exine and 3 distinct pores (*4*).

Powdered plant material

Flowering tops: Green or greyish-green. Fragments of stems, leaves, and bracts bearing rare glandular trichomes with a short stalk and a head formed of 2 rows of 3–5 cells enclosed in a bladder-like membrane and uniseriate covering trichomes consisting of 4–6 small, more or less isodiametric cells at the base and a thick-walled, often somewhat tortuous terminal cell, 400–1000 µm in length; fragments of the ligulate corolla with papillary epidermal cells; small-celled parenchyma from the corolla tubes containing cluster crystals of calcium oxalate; groups of lignified and pitted cells from the bracts; spherical pollen grains, about 30 µm in diameter, with 3 germinal pores and spiny exine; groups of sclerenchymatous fibres and small vessels with spiral or annular thickening, from the stem (*1*).

Aerial part: Greyish-green powder with epidermal fragments of stem and leaf with abundant covering trichomes and less numerous glandular trichomes, the covering trichomes frequently broken off and occurring scattered; groups of thick-walled, lignified fibres from the pericycle and xylem, those of the xylem sometimes associated with small vessels with spiral or annular thickening; lignified, pitted parenchyma from the pith;

dark brown fragments of the membranous margins of the bracts and groups of lignified and pitted elongated cells from the central region; occasional fragments of the papillose epidermis of the ligulate florets; small-celled parenchyma containing cluster crystals of calcium oxalate; pollen grains with a spiny exine (*4*).

General identity tests

Macroscopic and microscopic examinations (*1*, *3*, *4*), and thin-layer chromatography (*1*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*13*).

Foreign organic matter

Flowering tops: not more than 5% of stems with a diameter greater than 3 mm and not more than 2% of other foreign matter (*1*).
Aerial part: not more than 2% (*4*).

Total ash

Flowering tops: not more than 10.0% (*1*).
Aerial part: not more than 10% (*4*).

Acid-insoluble ash

Flowering tops: not more than 2.5% (*1*).
Aerial part: not more than 2.5% (*4*).

Water-soluble extractive

Aerial part: not less than 15.0% (*4*).

Loss on drying

Flowering tops: not more than 12.0% (*1*).
Aerial part: not more than 13% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*1*). For other pesticides, see the *European pharmacopoeia* (*1*)

and the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*13*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (*13*).

Chemical assays

Flowering tops: not less than 0.2% (v/w) of essential oil calculated on the basis of dried weight; and not less than 0.02% of proazulenes expressed as chamazulene by a combination of steam distillation and spectroscopic analysis (*1*).

Aerial part: not less than 0.1% (v/w) of essential oil determined by steam distillation (*3*).

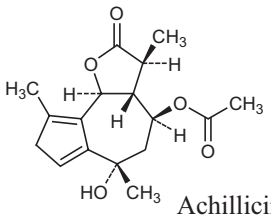
Major chemical constituents

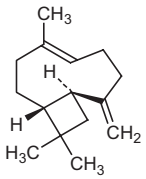
Contains 0.2–1.0% of essential oil. Being a chemically polymorphic aggregate plant species, the chemical constitution depends on the number of chromosomes present. Diploid and tetraploid plants contain proazulene sesquiterpenes, which when exposed to heat will be transformed to coloured azulenes, including chamazulene (up to 25%) and achillicin. Other major constituents in tetraploid plants include β-pinene (23%), α-pinene (5%) and caryophyllene (10–22%). Hexaploid plants are azulene sesquiterpene-free, and contain approximately 50% mono- and sesquiterpenes, many of which are in the oxidized form, as well as camphor (18%), sabinene (12%), 1,8-cineol (10%) and β-pinene (9%), among other constituents. Octaploid plants contain approximately 80% oxygen-containing monoterpenes, with linalool being the major constituent. Among the non-essential-oil constituents are flavonoids, coumarins and tannins (*6*, *7*, *9*, *11*, *15*). The structures of representative mono- and sesquiterpenes are presented below.

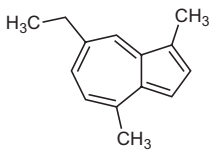
Medicinal uses

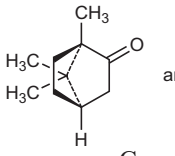
Uses supported by clinical data

None.

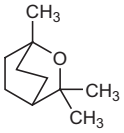

Achillicin

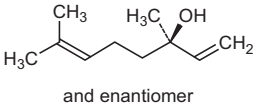

Caryophyllene


Chamazulene

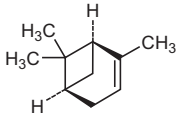

and enantiomer

Camphor

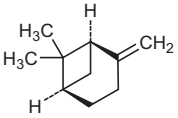

1,8-Cineole


and enantiomer

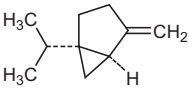
Linalool


and enantiomer

α-Pinene


and enantiomer

β-Pinene


and enantiomer

Sabinene

Uses described in pharmacopoeias and well established documents

Orally for loss of appetite, common cold, dyspeptic ailments such as mild spastic discomfort of the gastrointestinal tract, as a choleretic and for the treatment of fevers (*6*, *12*, *16*). Externally for skin inflammation and wounds (*6*).

Externally as a sitz bath for treatment of painful, cramp-like conditions due to menstrual disorders (*12*).

Uses described in traditional medicine

Orally as an emmenagogue, eyewash, haemostat, laxative, sleep aid, stimulant tonic, and to treat baldness, prostatitis and vertigo (*8*, *9*, *15*, *17*, *18*).

Used externally for the treatment of haemorrhoids, haematoma and burn injuries (*19*).

Pharmacology

Experimental pharmacology

Note: While the flowering tops of the plant are official in the *European pharmacopoeia* 2005 (*1*), much of the research on the pharmacology of this plant has been performed using the aerial parts of the plant, which

include the flowering tops. These data have been included and designated as coming from studies conducted on the aerial parts, but their direct applicability to the flowering tops needs to be further investigated.

Antibacterial activity

A 50% ethanol extract of the flowers inhibited the growth of *Shigella dysenteriae*, but not that of *Escherichia coli* or *Salmonella enteritidis*, in vitro at a concentration of 50 µl/agar plate (*20*). A methanol extract of the aerial parts inhibited the growth of 18 clinical strains of *Helicobacter pylori* in vitro, with a minimum inhibitory concentration of 50 µg/ml (*21*).

Anticonvulsant activity

Intraperitoneal injection of a 95% ethanol extract of the aerial parts to mice, at a dose of 2.0–4.0 ml/kg body weight (bw), had anticonvulsant activity against supramaximal electroshock- and corazol-induced convulsions, but was not effective against strychnine-induced convulsions (*22*).

Anti-inflammatory activity

In a study in mice, intraperitoneal injection of a fraction from an aqueous extract of the flower heads, at a dose of 40.0 mg/kg bw, inhibited yeast-induced pedal oedema (*23*). Intragastric administration of an 80% ethanol extract of the aerial parts to rats, at a dose of 100.0 mg/kg bw, inhibited carrageenan-induced pedal oedema by 29% (*24*). External application of a methanol extract of the aerial parts to mice, at a dose of 1.0 mg/ear, had weak anti-inflammatory effects (*25*). An aqueous extract of the aerial parts did not inhibit prostaglandin synthesis in microsomes at a concentration of 0.2 mg/ml (*26*). Santamarin, a sesquiterpene lactone from the crude drug, moderately inhibited the transcription of nuclear factor-kappa-beta, a protein that regulates the transcription of inflammatory mediators such as the cytokines and chemokines, at a concentration of 100 µM (*27*).

Antioxidant activity

Chamazulene, an artefact constituent of the aerial parts, inhibited cell membrane lipid peroxidation induced by Fe2+/ascorbate as assessed in the 2-thiobarbituric acid reactive assay. Chamazulene inhibited lipid peroxidation in a concentration- and time-dependent manner, with a median inhibitory concentration of 18 µM. It also inhibited the autoxidation of dimethylsulfoxide (33 mM) by 76% at 25 mM, and had a weak capacity to interact with 2,2-diphenyl-1-picrylhydrazyl (*28*).

Antipyretic activity
Oral administration of a hot aqueous extract or the juice of the aerial parts of the plant to rabbits, at a dose of 25 and 55 g/kg bw, respectively, reduced body temperature, while the 95% ethanol extract was not active (*29*).

Antispasmodic activity
An aqueous or methanol extract of the aerial parts of the plant (concentration not stated) inhibited contractions of rabbit small intestines in vitro (*30*).

Antiviral activity
A 50% methanol extract of the aerial parts inhibited HIV-1 reverse transcriptase in vitro at a concentration of 10% of the nutrient medium (*31*). Intraperitoneal administration of a hot-water extract of the dried flowers and leaves of the plant to mice (dose not stated) was active against tick-borne viral encephalitis (*32*).

Toxicology
Intraperitoneal administration of an aqueous extract of the aerial parts to rats had a median lethal dose of 1.5 g/kg bw (*33*). Intragastric or subcutaneous administration of an aqueous extract of the flowers to mice had a median lethal dose of > 1 g/kg bw (*33*).

Clinical pharmacology
Oral administration of a 70% ethanol extract of the flowers (dose not stated) increased the secretion of gastric juice in healthy volunteers by 178% (*16*). No further information on this study was available.

Adverse reactions
Numerous reports of allergic contact dermatitis have been published (*33–39*). In clinical testing, product formulations containing 2% of extracts of the crude drug were generally not irritating. In provocative testing, patients reacted to a Compositae mix that contained the crude drug, as well as to the crude drug alone. In clinical testing, a formulation containing 0.1% yarrow extract (propylene glycol and water) was not a sensitizer in a maximization test and alcoholic extracts of aerial parts of *A. millefolium* did not produce a phototoxic response (*33*).

A 5-year follow-up (1985–1990) of patients who were sensitive to Compositae showed that more than 50% reacted when tested with an ether extract of the plant, indicating cross-sensitivity (*35*). However, exacerbation of the patch test sites by irradiation with UV light was not ob-

served in any of the tested patients. One guaianolide compound, with a peroxide-bridged cyclopentane ring and an α-methylene-γ-butyrolactone structure, named α-peroxyachifolide, has been isolated from the flowers and appears to be responsible for the allergic contact dermatitis (*35*, *37*).

Therefore, direct contact with the crude drug or its preparations may cause hypersensitivity reactions of the skin or mucosa, such as rash, formation of vesicles and pruritus, in sensitive individuals.

Contraindications

Hypersensitivity to the plant and other Asteraceae (Compositae) (*12*, *40*, *41*). Gastric and duodenal ulcer, occlusion of the bile duct and gallbladder disease (*12*).

Due to the traditional use of the drug as an emmenagogue, it is contraindicated during pregnancy (*9*).

Warnings

Patients presenting with hypersensitivity or allergic reactions that include the formation of vesicles should stop treatment with Herba Millefolii immediately (*40*). If signs of hypersensitivity reaction reappear upon further use, the crude drug should not be used again.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A tincture of the crude drug was not mutagenic in the Ames test at a concentration of 160 µl/disc in *Salmonella typhimurium* strains TA98 and TA100. Metabolic activation had no effect on the results (*33*). An infusion of the aerial parts was tested for genotoxicity in the wing somatic mutation and recombination test (SMART) which makes use of the two recessive wing cell markers, multiple wing hairs (mwh) and flare (flr) on the left arm of chromosome 3 of *Drosophila melanogaster*. Three-day-old larvae, trans-heterozygous for these two markers, were fed the beverage (an infusion of *Achillea millefolium* (20 g/100 ml water) cooled and used immediately for the larval experiments) at different concentrations and for different feeding periods using *Drosophila* instant medium. Somatic mutations or mitotic recombinations induced in the cells of the wing imaginal discs gave rise to mutant single or twin spots on the wing blade of the emerging adult flies showing either the mwh phenotype and/or the flr phenotype. An infusion of *Achillea millefolium* was weakly genotoxic (*42*).

The results of previous investigations assessing the effect of the crude drug on reproduction have been contradictory. In one study, the addition

of the plant to the feed of rats, at a concentration of 25–50% w/w, suppressed the induction of estrus (*43*). However, oral administration of an extract of the leaves to rats did not alter the time of first mating, fertility or litter size (*44*). The effect of a 96% ethanol extract (200 mg/kg bw per day, intraperitoneally, for 20 days) and an 80% ethanol extract (300 mg/kg bw per day, orally, for 30 days) of the flowers on the spermatogenesis of Swiss mice was assessed by examining morphological characteristics with light and electron microscopes. Neither dose caused a significant difference in body weight gain or in the weight of the testes and seminal vesicles. The alterations observed were exfoliation of immature germ cells, germ cell necrosis, and seminiferous tubule vacuolization. Animals treated with the extracts had an increased number of metaphases in the germ epithelium that might be due to cytotoxic substances or substances stimulating cell proliferation (*45*).

Pregnancy: Non-teratogenic effects
See Contraindications.

Nursing mothers
Due to the lack of safety data the crude drug should not be used by breast-feeding mothers.

Paediatric use
Due to the lack of safety data the crude drug should not be used in children under the age of 12 years.

Other precautions
No information was found.

Dosage forms
Crude drug, extracts, fluidextract, infusions, succus (pressed juice from fresh herb) and tinctures.

Posology
(Unless otherwise indicated) (*12*)
Internal: 4.5 g of cut herb (flowering top) per day, or 3.0 g cut flowers for teas (infusions) and other Galenical preparations; pressed juice of freshly harvested herb.
Infusion: 1–2 g in 150 ml boiled water for 10–15 minutes, three times daily between meals.

Succus (pressed juice from fresh herb): 5 ml (1 teaspoon), three times daily between meals.
Fluidextract 1:1 (g/ml): 1–2 ml, three times daily between meals.
Tincture (1:5 g/ml): 5 ml, three times daily between meals.
External: sitz bath: 100 g per 20 litres of warm or hot water (*12*).

References

1. *European Pharmacopoeia*, 5th ed. Strasbourg, Directorate for the Quality of Medicines of the Council of Europe, 2005.
2. *Farmacopea homeopática de los estados unidos mexicanos*. Mexico City, Secretaría de Salud, Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, 1998 [in Spanish].
3. *The USSR State Pharmacopoeia,* 11th ed. Moscow, Meditsina, 1990.
4. *British herbal pharmacopoeia*. Exeter, British Herbal Medicine Association, 1996.
5. Duke JA. *Handbook of medicinal herbs*, 2nd ed. Boca Raton, FL, CRC Press, 2002.
6. Bradley PR, ed. *British herbal compendium. Vol. 1*. Dorset, British Herbal Medicine Association, 1992.
7. Wichtl M. *Herbal drugs and phytopharmaceuticals,* English ed. [Bisset NG, translated and edited], Boca Raton, FL, CRC Press, 1994.
8. de Padua LS, Bunyapraphatsara N, Lemmens RHMJ, eds. *Plant resources of South-East Asia,* No. 12(1). Leiden, Backhuys Publishers, 1999.
9. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005.
10. Bedevian AK. *Illustrated polyglottic dictionary of plant names*. Cairo, Medbouly Library, 1994.
11. Evans WC. *Trease and Evans pharmacognosy,* 15th ed. Edinburgh, WB Saunders, 2002.
12. Blumenthal M, Goldberg A, Brinckmann J, eds. *Herbal medicine. Expanded Commission E monographs*. Austin, TX, American Botanical Council, 2000.
13. *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues.* Geneva, World Health Organization, 2007.
14. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (WHO/FSF/FOS/97.7).
15. Rauchensteiner F, Nejati S, Saukel J. The *Achillea millefolium* group (Asteraceae) in Middle Europe and the Balkans: a diverse source for the crude drug Herba Millefolii. *Journal of Traditional Medicine*, 2004, 21:113–119.
16. Mahler P. Zur Wirkung der Bittermittel auf die Magensaftssekretion [The action of bitters on the secretion of gastric juice]. *Zeitschrift Gesamte Experimentelle Medizin*, 1926, 51:267–277 [in German].

17. *The Ayurvedic pharmacopoeia of India*, *Part I. Vol. I,* 1st ed. New Delhi, Government of India Ministry of Health and Family Welfare, Department of Indian Systems of Medicine and Homeopathy, 1990 (reprinted 2001).
18. Lesiovskaya EE et al, eds. *Pharmacotherapy with the principles of phytotherapy*. Moscow, Geotar-Med, 2003 [in Russian].
19. *Hagers Handbuch der Drogen* [CD ROM]. Heidelberg, Springer Verlag, 2003 [in German].
20. Caceres A et al. Plants used in Guatemala for the treatment of gastrointestinal disorders. 1. Screening of 84 plants against enterobacteria. *Journal of Ethnopharmacology*, 1990, 30:55–73.
21. Mahady GB et al. *In vitro* susceptibility of *Helicobacter pylori* to botanical extracts used traditionally for the treatment of gastrointestinal disorders. *Phytotherapy Research*, 2005, 19:988–991.
22. Athanassova SS, Roussinov K. Pharmacological studies of Bulgarian plants with a view to anticonvulsive effect. *Critical Reviews of the Academy of Bulgarian Sciences*, 1965, 18:691–694.
23. Goldberg AS et al. Isolation of the anti-inflammatory principles from *Achillea millefolium* (Compositae). *Journal of Pharmaceutical Sciences*, 1969, 58:938–941.
24. Mascolo N et al. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytotherapy Research*, 1987, 1:28–31.
25. Yasukawa K et al. Inhibitory effect of the methanol extracts from Compositae plants on 12-O-tetradecanoylphorbol-13-acetate-induced ear oedema in mice. *Phytotherapy Research*, 1998, 12:484–487.
26. Tunon H, Olavsdotter C, Bohlin L. Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis. *Journal of Ethnopharmacology*, 1995, 48:61–76.
27. Lyss G et al. A sesquiterpene and sesquiterpene lactones from the *Achillea millefolium* group possess anti-inflammatory properties but do not inhibit the transcription factor NF-κB. *Pharmaceutical and Pharmacological Letters*, 2000, 10:13–15.
28. Rekka EA, Kourounakis AP, Kourounakis PN. Investigation of the effect of chamazulene on lipid peroxidation and free radical processes. *Research Communications in Molecular Pathology and Pharmacology*, 1996, 92:361–364.
29. Nikonorow M. Investigation of the antipyretic action of native medicinal plants. *Acta Poloniae Pharmaceutica*, 1939, 3:23–56.
30. Hoerhammer L. Flavone concentration of medicinal plants with regard to their spasmolytic action. *Congress Scientifica Farmicia, Conference Communications*, 1962, 21:578–588.
31. Mlinaric A et al. Screening of selected plant extracts for *in vitro* inhibitory activity on HIV-1 reverse transcriptase (HIV-1 RT). *Pharmazie*, 2000, 55:75–77.
32. Fokina GI et al. Experimental phytotherapy of tick-borne encephalitis. *Soviet Progress in Virology*, 1991, 1:27–31.

33. Anonymous. Final report on the safety assessment of yarrow (*Achillea millefolium*) extract. *International Journal of Toxicology*, 2001, 20(Suppl 2):79–84.
34. Guin JD, Skidmore G. Compositae dermatitis in childhood. *Archives of Dermatology*, 1987, 123:500–502.
35. Hausen BM et al. alpha-Peroxyachifolid and other new sensitizing sesquiterpene lactones from yarrow (*Achillea millefolium* L., Compositae). *Contact Dermatitis,* 1991, 24:274–280.
36. Paulsen E, Andersen KE, Hausen BM. Compositae dermatitis in a Danish dermatology department in one year (I). Results of routine patch testing with the sesquiterpene lactone mix supplemented with aimed patch testing with extracts and sesquiterpene lactones of Compositae plants. *Contact Dermatitis*, 1993, 29:6–10.
37. Rucker G, Manns D, Breuer J. Peroxides as plant constituents. 8. Guaianolide-peroxides from yarrow, *Achillea millefolium* L., a soluble component causing yarrow dermatitis. *Archives of Pharmacology* (Weinheim), 1991, 324:979–981 [in German].
38. Schempp CM, Schopf E, Simon JC. Plant-induced toxic and allergic dermatitis (phytodermatitis). *Hautarzt*, 2002, 53:93–97 [in German].
39. Uter W et al. Occupational contact urticaria and late-phase bronchial asthma caused by compositae pollen in a florist. *American Journal of Contact Dermatitis*, 2001, 12:182–184.
40. Bisset NG, Wichtl M, eds. *Herbal drugs and phytopharmaceuticals*, 2nd ed. Stuttgart, Medpharm GmbH Scientific Publishers, 2001.
41. Rodrigues E, Towers GHN, Mitchell JC. Biological activities of sesquiterpene lactones. *Phytochemistry*, 1976, 15:1573–1580.
42. Graf U et al. Genotoxicity testing of different types of beverages in the Drosophila wing Somatic Mutation and Recombination Test. *Food and Chemical Toxicology*, 1994, 32:423–430.
43. de Laszlo H, Henshaw PS. Plant materials used by primitive peoples to affect fertility. *Science*, 1954, 119:626–631.
44. Barnes CS, Price JR, Hughes RL. An examination of some reputed antifertility plants. *Lloydia*, 1975, 38:135–140.
45. Montanari T, de Carvalho JE, Dolder H. Antispermatogenic effect of *Achillea millefolium* L. in mice. *Contraception*, 1998, 58:309–313.

Herba Origani

Definition

Herba Origani consists of the whole or cut dried aerial parts of *Origanum vulgare* L. (Lamiaceae), collected during the flowering phase (*1*).

Note: According to the *European pharmacopoeia*, Origani herba is the dried leaves and flowers separated from the stems of *Origanum onites* L. or *Origanum vulgare* L. subsp. *hirtum* (Link) Ietsw., or a mixture of both species (*2*).

Synonyms

Origanum angelicum Hill, *O. barcense* Simonk., *O. capitatum* Benth., *O. creticum* L., *O. dilatatum* Klokov, *O. elegans* Sennen, *O. floridum* Salisb., nom. illeg., *O. heracleoticum* L., *O. hortensis* Moensch, *O. latifolium* Mill., *O. nutans* Benth., *O. officinale* Gueldenst., *O. orientale* Mill., *O. prismaticum* (Gand.) Grossh., *O. puberulum* (Beck) Klokov, *O. purpurescens* Gilib., nom. inval., *O. thymiflorum* Rchb., *O. venosum* Benth., *O. virens* Guss. subsp. *siculum* Nyman, *O. watsonii* T. Schmidt & H. Schlag (*3–7*).

Selected vernacular names

Acciughero, aitz belarr, anrar, ào lè gāng, ào lè gāng cǎo, avishan kuhi, bantulsi, bergminta, bergmynte, brauner dost, brauner dosten, buklutulgezal, ching chieh, common marjoram, dobromysl, dost, doste, dosten, duhov'i tsvet, dushita, dushitsa, dziki majeranek, echter dost, erba acciuga, fekete gyopár, frauendost, gemeiner dost, Gewöhnlicher Dost, hanahakka, harilik pune, herba origani, jakhmbuti, kaslók, kekik otu, klopovnaya trava, kostets, kostolomnaya trava, kung, kungsmynta, lepiodka pospolita, loragiño, majurano fero, marjolaine bâtarde, marazolette, marijolai, marjolaine sauvage, marjolaine sauvage origan, marzangush, materynka, materynka zvichajna, mountain mint, mravinac, mäkimeirami, ngàuh ji, ngou lahk gòng, niu zhi, oragan, ordinara origano, oregano, oregáno, orégano, oreganó, oregánó, orégão, oregâos, orenga, organ, oreganos, organy, origan, origan commun, origan vulgaire, origano, orig-

anum, ourego, paprastasis raudonėlis, pamajorán obyčajný, pelevoué, penevoué, pot oregano, raudenes, remago, rigan, riegnu, rigon i egër, rijan, rigoni i zakonshëm, satar barri, sathra, sovârf, szurokfű, tavshava, thé rouge, thym de berger, tograihon, tost, vadmajoránna, vild mejram, wild marjoram, wild oregano, wilde marjolein, wilder majoran, winter marjoram, wintersweet (*3–5*, *7–21*).

Geographical distribution

The plant is commonly distributed throughout Asia, Europe and northern Africa. It is native to Europe and the Middle East. In the Newly Independent States, it grows in the European areas, also in Caucasus, Central Asia and western Siberia (*8*, *19*, *22–25*).

Description

A perennial herbaceous plant, 30–90 cm high. Rhizome, horizontal, creeping. Stems, erect, woody at the base, branched, quadrangular, hairy, often violet or purplish-green. Leaves, opposite, petiolate, ovate, rounded at the base, subserrate, sometimes toothed, entire-margined or slightly crenate, glabrous or hirsute, translucent punctate, green on both sides, paler underneath, 10–40 mm long, 4–25 mm wide; petiole hairy, about one fourth as long as the leaves. Inflorescence, corymb-like inflorescences at the branch apexes. Flowers, labiate type, generally bisexual, sometimes just female flowers with immature stigmas, zygomorphic, with short peduncle. Bracts elliptical, pointed, longer than calyx, dark purple. Calyx, generally 5-lobed, radial to bilateral, sepals triangular lanceolate, with 13 veins, about 3 mm long, with a hairy ring inside. Corolla, upper lip flat, lower lip has 3 lobes, from pink or purple to white, about 6 mm long. Stamens 4, exserted, didynamous, with double anthers. Pistil, stigma bifid and reflexed. Fruit, nutlets, oval to ovate, in persistent calyx, dry, smooth, dark brown, 0.5–1 mm long (*4*, *8*, *14*, *17*, *25–29*).

Plant material of interest: dried aerial parts

General appearance

The drug consists of flowering leafy stems up to 20 cm long, green or violet in colour (*1*). The leaves are opposite, petiolate, ovate or ovate-elliptic; the margins are entire or serrate; the apex is acute or obtuse; upper surface green, lower surface paler; 20–40 mm long. Flowers are rare, 3–5 mm long, found as unbroken or broken parts of the corymbs. Bracts are dark purple and imbricate. Calyx is tubulous, 5-sepalled, co-

rolla-like, glabrous or lightly hairy, inconspicuous. Corolla of labiate type, white or violet (*1*, *2*).

Organoleptic properties

Odour: aromatic; taste: slightly bitter, spicy and astringent (*1*).

Microscopic characteristics

The stem is quadrangular in transverse section, with rectangular epidermal cells; 1-layered collenchyma underlying epidermis and 3-layered one in each corner of the stem. A broken ring of fibres and few stone cells in cortex; cortex cells with brown content in about 3 layers of cells adjoining phloem tissue. Leaf: the cells of leaf epidermis are sinuous (much more so on the underside), with regularly or sometimes irregularly thickened walls. The epidermis is covered by a thin cuticle. Diacytic stomata more frequent on the lower epidermis. Simple and glandular trichomes on both epidermises, preponderant on the lower one. The simple trichomes are curved, pointed, 1–5 celled, rugous. Glandular trichomes with 1–3-cellular stalk and unicellular head. The secretory glands are 8–12-celled, mainly on the lower side of leaves. Petiole with isodiametric or rectangular epidermal cells; simple and glandular trichomes; collenchyma tissue in corners and partly underlying upper and lower epidermis; central vascular bundle. Flower bracts and calyx have similar structure to the leaf but in the calyx there are no hairs on the inner epidermis. The corolla tube has irregular cells in the inner lobe and is regular and papillose towards and at lobes (*1*, *30–32*).

Powdered plant material

The powder is green. When examined under a microscope, the covering trichomes are of lamiaceous type or short, unicellular and rarely conical; conical trichomes are shaped like pointed teeth; covering trichomes are thick-walled and contain minute needles. Cuticle of covering trichomes is warty. The epidermises of the leaves have cells with sinuous walls; diacytic stomata; cells of the upper epidermis are beaded; secretory trichomes with 8–12 cells; glandular trichomes are rare, they have a unicellular head and bicellular or tricellular stalk; pollen grains are smooth, spherical and abundant (*2*).

General identity tests

Macroscopic and microscopic examinations (*1*, *2*), and thin-layer chromatography tests for the characteristic volatile oil constituents, thymol and carvacrol (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*33*).

Chemical

No information available.

Foreign organic matter

Not more than 2% (*2*). Not more than 1%. Not more than 7% fragments of the brownish and blackish herb. Not more than 40% of stems. For cut drug: not more than 10% of fragments of drug having a diameter less than 0.5 mm and not more than 10% of fragments of drug having a diameter more than 7 mm (*1*).

Total ash

Not more than 15% (*2*). Not more than 10% (*1*).

Acid-insoluble ash

Ash insoluble in hydrochloric acid must not be more than 4% (*2*).

Sulfated ash

No information available.

Water-soluble extractive

No information available.

Alcohol-soluble extractive

No information available.

Loss on drying

Not more than 13% (*1*). Maximum water content, 120 ml/kg, determined on 20.0 g of the powdered drug (*2*).

Pesticide residues

The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*) and the WHO guidelines on quality control methods for medicinal plant materials (*33*) and pesticide residues (*34*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*33*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*33*) for the analysis of radioactive isotopes.

Other purity tests

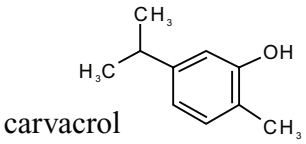
The content of mineral matter must not be more than 1% (*1*). Chemical, sulfated ash, alcohol-soluble extractive and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

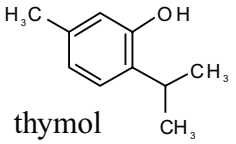
Herba Origani contains not less than 2.5% of volatile oil and a minimum of 1.5% carvacrol and thymol in anhydrous drug. Volatile oil is quantitatively determined by distillation, and the percentage content of phenols is determined by gas chromatography (*2*). Whole Herba Origani contains not less than 0.1% volatile oil. The cut drug contains not less than 0.08% of volatile oil (*1*).

Major chemical constituents

Herba Origani contains 0.15–1.2% of volatile oil. The chief components of the volatile oil are carvacrol (40–70%), γ–terpinene (8–10%), p-cymene (2.80–10.00%), as well as α-pinene, myrcene, thymol, α-terpinene, estragole, eugenol and (E)-β-ocimene, among others. There are also strains that contain thymol, linalool with terpinen-4-ol, linalool, β-caryophyllene, germacrene D and sabinene as the major components. The ethanol-water extract contains flavonoids (naringin, luteolin-7-glucoside, diosmetin-7-glucoside and apigenin-7-glucoside), rosmarinic acid (approximately 5%) and other phenolic esters; tannins are also present (*4*, *7*, *8*, *17*, *19*, *24*, *35*–*38*). The structures of the main characteristic constituents are presented below.



carvacrol



thymol

Medicinal uses

Uses supported by clinical data

No information was found.

Uses described in pharmacopoeias and well established documents

No information was found.

Uses described in traditional medicine

Herba Origani is used to treat cough, colds and bronchial catarrh, and is used as an expectorant and diaphoretic (*39–41*). Other uses include the treatment of bloating, stimulation of bile secretion, of the appetite and of digestion, and as a sedative and antispasmodic agent (*15*, *42*, *43*). Herba Origani is also used as an emmenagogue in Unani medicine (*44*), and for treatment of algomenorrhoea and impotence (*45*). The herb is used as a diuretic and as a treatment for kidney infections, kidney stones and poor renal function resulting from chronic nephritis (*22*). It is also used to treat inflammation, arthritis (*46*), hepatitis (*47*, *48*), and externally for scrofula and wound healing (*49*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

An ethanol extract (80%) of Herba Origani at a concentration of 250 µg/ml/agar plate was active against *Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Salmonella typhi, Staphylococcus aureus* and *Streptococcus hemolyticus* in vitro. Using a disc diffusion method, the extract dissolved in dimethyl sulfoxide at a concentration of 4.0 µg/disc, exhibited antibacterial activity against *Bacillus subtilis*. The inhibition halos in the same test (4.0 µg/disc) were: *Klebsiella pneumoniae* and *Proteus mirabilis* 4 mm, *Salmonella typhi* 8 mm, *Staphylococcus aureus* 6 mm, *Streptococcus hemolyticus* 14 mm, and *Escherichia coli* 20 mm. The essential oil of the dried leaf demonstrated antibacterial activity at a concentration of 150.0 ppm against a broth culture of *Lactobacillus plantarum* and *Leuconostoc mesenteroides* (*50*).

The aqueous ethanol extract (1:1) of the dried entire plant at a concentration of 500 mg/ml/agar plate (dose expressed as dry weight of plant) demonstrated weak antifungal activity against *Aspergillus fumigatus, Aspergillus niger, Botrytis cinerea, Fusarium oxysporum, Penicillium digitatum, Rhizopus nigricans, Trichophyton mentagrophytes*, and antiyeast activity against *Candida albicans* and *Saccharomyces pastorianus* (*51*). The

essential oil of the aerial parts of the plant exhibited a strong antifungal effect at a concentration of 100.0 ppm/agar plate against *Gloeosporium album, Phytophthora nicotianae, Botrytis cinerea, Helminthosporium teres, Monilia laxa* and *Phytophthora infestans* (*52*). The essential oil also inhibited the growth of *Cryptococcus neoformans* at a minimum inhibitory concentration of 150 µl/l/agar plate and inhibited the growth of *Candida albicans* by 0.12% (*53*, *54*). The essential oil of the leaf (0.25 and 1 µl/ml/agar plate) inhibited the growth of *Trichophyton rubrum, Trichosporon beigelii* and *Malassezia furfur* (*55*).

Antiviral activity

A 10% aqueous extract of the aerial parts of the plant demonstrated antiviral activity in cell culture against herpes simplex virus (HSV-2), influenza virus A2 (Mannheim 57) and vaccinia virus (*56*).

Insecticide activity

The essential oil of the aerial parts of the plant (concentration 20 µg) caused complete sterility in *Dysdercus koenigii* (*57*), and topical application of the oil demonstrated insecticidal properties (20 µl of stock solution of origanum oil) against *Drosophila auraria* adults, eggs and larvae (*58*). The median lethal dose for *Drosophila melanogaster* was determined to be 6.78 µl of stock solution of origanum oil by the somatic mutation and recombination test (*59*).

Antiparasitic activity

The essential oil of the fresh leaves of the plant (1 mg/l) acted as an antinematodal agent against *Meloidogyne javanica* (*60*).

Anti-inflammatory effects

The methanol extract of *Origanum* leaf applied externally to mice (20 µl/animal) exhibited anti-inflammatory effects in animals with ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate (*61*). Similarly, the external application of a methanol extract of *Origanum* leaf to mice in vivo at a dose of 2 mg/ear inhibited ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate with an index of inhibition of 27 (*62*).

Antioxidant activity

A tannin fraction and an ethanol-aqueous extract (1:1) of the dried flowering top and leaf of *Origanum vulgare* exhibited strong antioxidant activity in vitro. The free-radical scavenging effect of the tannin fraction on 1,1-diphenyl-2-picrylhydrazyl was estimated to occur at a median effec-

tive dose of 16.2 mg/ml. The median effective dose for the antioxidant activity of the ethanol-aqueous extract was estimated to be 16 mg/ml as assessed by a colorimetric assay (*63*, *64*). In addition, the antioxidant activity of the diethyl ether extract of dried leaves of *Origanum vulgare* (concentration 0.02%) was demonstrated when assayed against corn oil, soybean oil and olive oil (*65*). The water-soluble active ingredients were isolated, and their structures were determined. Over 70% radical scavenging activity was found for two of them – rosmarinic acid and 4´-*O*–β-D-glucopyranosyl-3´,4´-dihydroxybenzyl protocatechuate – when applied at 2×10^{-5} M in the 1,1-diphenyl-2-picrylhydrazyl test (*66*).

Antihyperglycaemic activity

An aqueous extract of dried leaves of *Origanum vulgare* exhibited antihyperglycaemic activity in vivo when administered to rats by the intragastric route at a dose of 20 mg/kg body weight (bw) (*46*). Commercial samples of *Origanum* leaf (concentration 12.5 mg/ml) exhibited insulin potentiating effects in vitro (*67*).

Antimutagenic activity

The aqueous and methanol extracts of dried and fresh leaves of *Origanum vulgare* exhibited desmutagenic activity in an in vitro model, at a concentration of 10 µg/agar plate of *Salmonella typhimurium* TA98, against 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole-induced mutagenesis (*68*). Both the essential oil and carvacrol were shown to strongly inhibit mutagenicity induced by 4-nitro-o-phenylenediamine and 2-aminofluorene in the presence or absence of a metabolic activator, which would suggest a protective effect against cancer (*69*).

Toxicology

In mice, the median lethal dose for an aqueous-ethanol extract (1:1) of the entire plant has been recorded as > 1 g/kg (by intraperitoneal injection) (*70*). The essential oil of the aerial parts of the plant, at a concentration of 0.01%, inhibited proliferation of rabbit epidermal CA-HEP-2 cells, Vero cells, and cultured HeLa cells (*71*).

Clinical pharmacology

No information was found.

Adverse reactions

No information was found.

Contraindications

If signs of hypersensitivity reactions appear (rash, pruritus, urticaria, swelling of mouth and skin) Herba Origani must not be used again.

Precautions

General

No information was found.

Drug and laboratory test interactions

No information was found.

Carcinogenesis, mutagenesis, impairment of fertility

No information was found.

Pregnancy

Ingestion of strong (concentrated) teas made with Herba Origani may cause uterine contractions. Women should avoid taking the herb during pregnancy and lactation (*72*).

Nursing mothers

See Pregnancy.

Paediatric use

No information was found.

Drug interactions

No information was found.

Dosage forms

Comminuted herb for infusion.

Posology

(Unless otherwise indicated)

Internal use. As an infusion: one tablespoon of an infusion (10 g of dried herb in 200 ml boiling water for 15–20 minutes) three times daily before meals (*73*). Tincture: 1 ml of a tincture (10 g of dried herb in 150 ml 70% ethanol) three times daily (*74*).

External use. As a compress, cataplasm or gargle: add 20–30 g of herb to 200 ml of boiling water for a direct application (*75*).

References

1. *USSR pharmacopoeia*, 11th ed. *Vol. 2*. Moscow, Meditsina, 1990.
2. *European pharmacopoeia*, 5th ed. suppl. 5.2. Strasbourg, European Pharmacopoeia Commission, 2005.
3. *Northern Ontario plant database* (http://www.northernontarioflora.ca/).
4. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific Publishers, 2001.
5. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.
6. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005 (http://www.napralert.org).
7. Wren RC. *Potter's new cyclopaedia of botanical drugs and preparations.* Essex, CW Daniel, 1975.
8. Fleming T, ed. *Physicians desk reference (PDR) for herbal medicines*. Montvale, Medical Economics Company, 2000.
9. Kerbabajev BB. *Narodn'je I nautshn'je Turksmenskije nazvanija rasteni*. Ashabat, 'l'm, 1992.
10. *Gernot Katzer's spice pages* (http://www.uni-graz.at/~katzer/engl/).
11. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
12. *Henriette's plant name search* (http://www.henriettesherbal.com/php/index.php).
13. Caius FJR. *The medicinal and poisonous plants of India.* Jodhpur, Scientific Publishers, 2003.
14. Kirtikar KR, Basu BD. *Indian medicinal plants.* In 4 vols. Delhi, M/S Bishen Singh Mahendra Pal Singh, 1918.
15. Turova AD, Sapozhnikova EN. *Lekarstvennie rastenija SSSR i ikh primenenie*. Moscow, Meditsina, 1982.
16. Grigorescu E, Ciulei I, Ursula S. *Index fitoterapeutic.* Bucharest, Editura Medicala, 1986.
17. Chauhan NS. *Medicinal and aromatic plants of Himachal Pradesh.* New Delhi, Indus Publishing Company, 1999.
18. Parsa A. *Flore de L'Iran*. *Vol. VIII*. Tehran, University of Tehran, 1960.
19. HagerROM 2004. *Hagers Handbuch der Drogen und Arzneistoffe.* Heidelberg, Springer Verlag, 2005.
20. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
21. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
22. Chevallier A. *The encyclopaedia of medicinal plants*. London, Dorling Kindersley, 1996.
23. *Plants for a future* (http://www.ibiblio.org/pfaf/D_search.html).

24. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
25. Yakovlev GP, Blinova KF, eds. *Lekarstvennoje rastitel'noje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
26. Gardner JA. *Herbs in bloom: A guide to growing herbs as ornamental plants.* Portland, OR, Timber Press, 1998.
27. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR*. 3-ie izd. Kishinev, Shtiintsa, 1986.
28. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR.* Izd. Moscow, Mysli, 1976.
29. Alexeev IE et al. *Travianistye rastenia SSSR. Vol. 2.* Izd. Moscow, Mysli, 1971.
30. *Homoeopathic pharmacopoeia of India*. *Vol. 6*. Government of India, Ministry of Health and Family Welfare, 1990.
31. Toma C, Rugina R. *Anatomia plantelor medicinale. Atlas***.** Bucharest, Editura Academiei Romane, 1998.
32. Grinkevici NI, Ladiginoi EI. *Pharmacognozia. Atlas. Pod red.* Moscow, Meditsina, 1989.
33. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
34. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
35. Yakovlev GP, Blinova KF, eds. *Rastenija dlja nas.* St Petersburg, Utchebnaja kniga, 1996.
36. Ivask K et al. Composition of the essential oil from wild marjoram (*Origanum vulgare* L. ssp. *vulgare*) cultivated in Estonia. *Journal of Essential Oil Research*, 2005, 17:384–387.
37. Mockute D, Bernotiene G, Judzentiene A. The essential oil of *Origanum vulgare* L. ssp. *vulgare* growing wild in Vilnius district (Lithuania). *Phytochemistry*, 2001, 57:65–69.
38. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Magnoliaceae-Limoniaceae. Vol. 6*. Leningrad, Nauka, 1991.
39. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
40. Zargari A. *Medicinal plants,* 5th ed., *Vol. 4.* Tehran, Tehran University, 1992:969.
41. De Feo V et al. Traditional phytotherapy in the peninsula Sorrentina, Campania, Southern Italy. *Journal of Ethnopharmacology*, 1992, 36:113–125.
42. Anonymous. *The herbalist*. Hammond, IN, Hammond Book Company, 1931.
43. Novaretti R, Lemordant D. Plants in the traditional medicine of the Ubaye valley. *Journal of Ethnopharmacology,* 1990, 30:1–34.
44. Yesilada E et al. Traditional medicine in Turkey. V. Folk medicine in the Inner Taurus mountains. *Journal of Ethnopharmacology*, 1995, 46:133–152.

45. Mikhailenko ET, Radzinskii WE, Zakharov KA. *Lekarstvennye rastenija v akusherstve I ginekologii,* 2nd ed. Kiev, Zdorovje, 1987.
46. Mascolo N et al. Biological screening of Italian medicinal plants for antiinflammatory activity. *Phytotherapy Research*, 1987, 1:28–31.
47. Lin CC, Kan WS. Medicinal plants used for the treatment of hepatitis in Taiwan. *American Journal of Chinese Medicine*, 1990, 18:35–43.
48. Lemhadri A et al. Anti-hyperglycaemic activity of the aqueous extract of *Origanum vulgare* growing wild in Tafilalet region. *Journal of Ethnopharmacology*, 2004, 92:251–256.
49. De Feo V, Senatore F. Medicinal plants and phytotherapy in the Amalfitan coast, Salerno province, Campania, Southern Italy. *Journal of Ethnopharmacology*, 1993, 1:39–51.
50. Kivanc M, Akgul A, Dogan A. Inhibitory and stimulatory effects of cumin, oregano and their essential oils on growth and acid production of *Lactobacillus plantarum* and *Leuconostoc mesenteroides. International Journal of Food Microbiology*, 1991, 13:81–85.
51. Guerin JC, Reveillere HP. Antifungal activity of plant extracts used in therapy. II. Study of 40 plant extracts against nine fungi species. *Annales Pharmaceutiques Françaises*, 1985, 43:77–81.
52. Bourrel C et al. Chemical analysis and fungistatic properties of some essential oils in a liquid medium. Effects on hyphal morphogenesis. *Rivista Italiana Eppos*, 1995, 6:31–42.
53. Viollon C, Chaumont JP. Antifungal properties of essential oils and their main components upon *Cryptococccus neoformans*. *Mycopathologia*, 1994, 128:151–153.
54. Hammer KA, Carson CF, Riley TV. *In-vitro* activity of essential oils, in particular *Melaleuca alternifolia* (tea-tree) oil and tea tree oil products, against Candida spp. *Journal of Antimicrobial Chemotherapy*, 1998, 42:591–595.
55. Adam K et al. Antifungal activities of *Origanum vulgare* subsp. hirtum, *Mentha spicata, Lavandula angustifolia,* and *Salvia fruticosa* essential oils against human pathogenic fungi. *Journal of Agricultural and Food Chemistry*, 1998, 46:1739–1745.
56. May G, Willuhn G. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. *Arzneimittel-Forschung,* 1978, 28:1–7.
57. Koul O, Tikku K, Saxena BP. Ovarian dysfunction and morphogenetic defects induced by *Origanum vulgare* L. oil in the red cotton bugs. *Current Science*, 1987, 56:1025–1028.
58. Konstantopolou I et al. Insecticidal effects of essential oils. A study of the effects of essential oils extracted from eleven Greek aromatic plants on *Drosophila auraria. Experientia*, 1992, 48:616–619.
59. Karpouhtsis I et al. Insecticidal and genotoxic activities of oregano essential oils. *Journal of Agricultural and Food Chemistry*, 1998, 46:1111–1115.

60. Oka Y et al. Nematicidal activity of essential oils and their components against the root-knot nematode. *Phytopathology*, 2000, 90:710–715.
61. Okuyama T et al. Studies on cancer bio-chemoprevention of natural resources. X. Inhibitory effect of spices on TPA-enhanced 3H-choline incorporation in phospholipid of C3H10T1/2 cells and on TPA-induced ear edema. *Zhonghua Yaoxue Zazhi*, 1995, 47:421–430.
62. Yasukawa K et al. Inhibitory effect of edible plant extracts on 12-O-tetradecanoylphorbol-13-acetate-induced ear oedema in mice. *Phytotherapy Research*, 1993, 7:185–189.
63. Lamaison JL, Petitjean-Freytet C, Carnat A. Rosmarinic acid, total hydroxycinnamic derivative contents and antioxidant activity of medicinal Apiaceae, Boraginaceae and Lamiaceae. *Annales Pharmaceutiques Françaises*, 1990, 48:103–108.
64. Lamaison JL, Petitjean-Freytet C, Carnat A. Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid. *Pharmaceutica Acta Helvetiae*, 1991, 66:185–188 [in French].
65. Vekiari SA et al. Oregano flavonoids of lipid antioxidants. *Journal of American Oil Chemists Society*, 1993, 70:483–487.
66. Matsuura H et al. DPPH radical scavengers from dried leaves of oregano (*Origanum vulgare*). *Biosciences, Biotechnology, Biochemistry,* 2003, 67:2311–2316.
67. Broadhurst CL, Polansky MM, Anderson RA. Insulin-like biological activity of culinary and medicinal plants aqueous extracts in vitro. *Journal of Agricultural and Food Chemistry*, 2000, 48:849–852.
68. Kanazawa K et al. Specific desmutagens (antimutagens) in oregano against a dietary carcinogen, TRP-P-2, are galangin and quercetin. *Journal of Agricultural and Food Chemistry,* 1995, 43:404–409.
69. Ipek E et al. Genotoxicity and antigenotoxicity of origanum oil and carvacrol evaluated by Ames Salmonella/microsomal test. *Food Chemistry*, 2005, 93:551–556.
70. Bhakuni OS et al. Screening of Indian plants for biological activity. Part II. *Indian Journal of Experimental Biology,* 1969, 7:250–262.
71. Sivropoulou A et al. Antimicrobial and cytotoxic activities of origanum essential oils. *Journal of Agricultural and Food Chemistry*, 1996, 44:1202–1205.
72. Ciganda C, Laborde A. Herbal infusions used for induced abortion. *Journal of Toxicology and Clinical Toxicology*, 2003, 41:235–239.
73. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.
74. Ladynina EA, Morozova RS. *Fitoterapija*. Leningrad, Meditsina, 1987.
75. Lager AA. *Fitoterapija*. Krasnojarsk, Izdatel'stvo krasnojarskogo universiteta, 1988.

Herba Pegani harmalae

Definition

Herba Pegani harmalae consists of the dried aerial parts of *Peganum harmala* L. (Zygophyllaceae), collected during the flowering season (*1–3*). The seeds of *P. harmala* are used in traditional medicine (*4–6*).

Synonyms

Peganum multisectum Maxim. (*1*).

Selected vernacular names

Adrashman, African rue, armel, aspand, bender tiffin en tamachek, besasa, bizr el hharmel, churma, epnubu, esfand, espand, gandaku, garmala ob'knovennaya, gemeine syrische Raute, ghalqat edh dhi'b, haoma, harale, harilik peeganum, harmal, harmala, harmale, harmalkraut, harmal rutbab, harmel, harmel sahari, harmara, harmaro, hermal, hermale, hermel, Hermelkraut, hermelraute, hharmal, hom, hormol, hurmaro, hurmul, hurmur, hurmuro, isband, isbaend-lahouri, isirik, isiriq, isbendlahouri, ispand, ispand lahouri, ispanthan, ispun, kaladana, khokrana, kisankur, lahouri-hurmul, l'harmel, mahmur çiç, mariamsakmela, mogilnik, moly, mountain rue, pégane, pegano, peganum, rue, rue sauvage, rue verte, sadhab barri, sadhâb barrí, sarmala, sauvage, shimai-aravandi-virati, shimai-azha-vanai-virai, simagoranta, simaiyalavinai, sima-goronti, sime-goranti, sipand, spail-anai, spand, spanda, spanj, spélanè, steppenraute, Syrian rue, syrische Raute, ruin weed, ruta della siria, ruta salvatica, sipend, spand, stepnaya ruta, techepak, tukhum-i-isfand, turetskaya kraska, uzarih, vilayati-isband, vilayati-mhendi, wild raute, wild rue, üzerlik otu (*7–21*).

Geographical distribution

Native to the Middle East, North Africa and southern Europe, Herba Pegani Harmalae is naturalized in other subtropical regions, including Australia. In the Newly Independent States, it grows in Central Asia, and also in the Caucasus (*5*, *14*, *19*, *22*).

Description

A perennial plant, 30–100 cm high. Rhizome, woody, large. Root, stout. Stems, numerous, herbaceous, shrubby base, branched, forked-corymbose, glabrous. Leaves, alternate, sessile, ovate outline, 4–10 cm long, 5.8–6.5 cm wide, irregularly finely divided into long narrow lobes of 1–3.5 cm long and 1.5–3 mm wide. Inflorescence, compound monochasial scorpioid cyme. Flowers, terminal and axillary, solitary, actinomorphous, hermaphrodite, white, fragrant, 25–30 mm in diameter; pedicels angular, green, 1–2.5 cm long; petals 5, oblong-elliptic; sepals 5, persistent, narrow, slightly longer than the petals; stamens 10–15, enlarged at the base filaments; ovary globular, trilocular, superior. Fruits, capsules, globular, stalked, erect, 3-valved loculicidal, 6–10 mm in diameter, dull earthy brown colour, reticulate seed coat, strong characteristic odour when crushed, bitter in taste. Seeds, numerous (more than 50), subtriangular, reticulately pitted, 3–4 mm long, dark brown. The herbage begins to develop new shoots in February, flowers appear in April, the plant flowers until October and bears fruits from April to November. The aerial parts are gathered in summer (*1*, *3*, *7*, *17*, 23–*27*).

Plant material of interest: dried aerial parts

General appearance

Fragments of young stems, cylindrical, glabrous, 8–80 mm long, up to 8 mm in diameter, yellowish-green. Whole or fragmented leaves, filiform, glabrous, 0.5–20 mm long, yellowish or brownish-green. Flowers large, terminal, and white. The seeds are triangular concavo-convex, dull brown, up to 4 mm long and 1–2 mm broad (*14*, *22*).

Organoleptic properties

Odour: specific, slight, unpleasant; taste (of fruits): very bitter, spicy (*4*, *28*).

Microscopic characteristics

Leaf has two kinds of epidermal cells: large oblong and small isodiametric. Anomocytic stomata surrounded by small epidermal cells. Needle-like calcium oxalate crystals in the mesophyll. Glandular trichomes on the whole upper epidermis of young leaves persisting only at the leaf base at maturity. Trichomes have a stalk of 4–6 cells and a multicellular head. Seed rind is 4-layered. Outer layer of epidermis consists of large, rectangular, radially elongated (the length being two to three times greater than the breadth), thick-walled cells, strongly thickened in the upper corners and with outgrowth of walls starting from the inside. Epidermal cells

contain mucilage. Parenchyma layer beneath epidermis is usually formed of 3–4 rows of small air-filled cells; a dark brown layer of disintegrated cells, wavy in appearance; elongated thin-walled cells containing a yellowish brown substance, which gives a positive test for fixed oil. Endosperm made up of polygonal cells with uniformly thickened cellulose cell membranes. The endosperm of seed-lobe area is formed of 7–8 layers of cells and endosperm of rootlet area of 2–3 layers of cells. The germ is slightly bent and consists of 2 equally mature cotyledons, budlet, short hypocotyl and well-marked rootlets with forming root caps (*14*, *22*, *29*).

Powdered plant material

No information available.

General identity tests

Macroscopic and microscopic examinations (*24*, *28*), and thin-layer chromatography to be established in accordance with national requirements. A high-performance liquid chromatography method for the determination of specific alkaloids in the seeds has been developed and validated (*30*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*31*).

Chemical

No information available.

Foreign organic matter

Not more than 4% (*28*). Not more than 2% (*24*). Maximum 10% fragments of stems longer than 80 mm. Not more than 5% of greyish stems of previous year. Not more than 5% of fragments of drug having a diameter less than 0.315 mm (*28*).

Total ash

Not more than 18% (*28*). Not more than 10% (*24*).

Acid-insoluble ash

No information available.

Sulfated ash
No information available.

Water-soluble extractive
No information available.

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 12% (*28*). Not more than 10% (*24*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*32*). For other pesticides, see the *European pharmacopoeia* (*32*) and the WHO guidelines on quality control methods for medicinal plant materials (*31*) and pesticide residues (*33*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*31*).

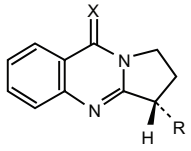
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*31*) for the analysis of radioactive isotopes.

Other purity tests
The content of mineral matter is not more than 2% (*28*). Chemical, acid-insoluble ash, sulfated ash, alcohol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

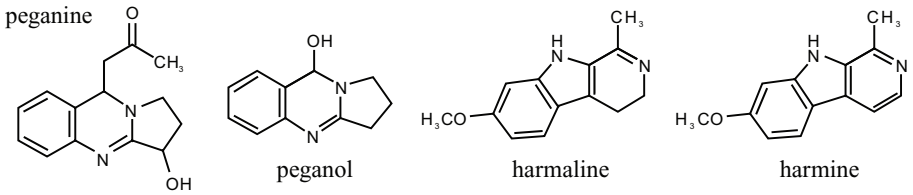
Chemical assays
Aerial parts contain not less than 1.5% alkaloids (*28*). A high-performance liquid chromatography method for the analysis of specific alkaloids in the seeds has been developed and validated (*30*).

Major chemical constituents
The major constituents of the dried aerial parts are indole alkaloids which dominate during and after flowering when harmine and harmaline pre-

dominate. Other major alkaloids are harmolol (harmol) and peganine. Harmine is present in all parts of the plant. On isolation it forms colourless crystals. The alkaloid (–)-peganine (vasicine) occurs in blossoms and stems. The aerial parts contain 0.77%, leaves 0.3–0.4% and seeds contain 3.5–6% alkaloids (including 60% harmaline and 30% harmine) (*22*, *30*, *34–39*). Several other alkaloids (among them dipegine, dipeginol and tetrahydroharmine), and four flavonoid glycosides (acacetin-7-*O*-rhamnoside, acacetin-7-*O*-[6´´-*O*-glucosyl-2´´-*O*-(3´´´-acetylrhamnosyl)]glucoside, acacetin-7-*O*-[2´´-*O*-rhamnosyl-2´´-*O*-glucosyl]glucoside and the glycoflavone 2´´´-*O*-rhamnosyl-2´´-*O*-glucosylcytisoside) have been isolated from the drug (*40*, *41*). Also present are quinazoline alkaloids with a similar structure: vasicinone, pegaline, tetrahydroharman and desoxyvasicinone (*17*) together with saponins, tannins and organic acids (*22*). The structures of some characteristic constituents are presented below.



I-Peganine	R = OH	X = H_2	(-)-isomer
dl-Peganine	R = OH	X = H_2	racemic
Desoxypeganine	R = H	X = H_2	
I-Vasicinone	R = OH	X = O	(-)-isomer
dl-Vasicinone	R = OH	X = O	racemic
Desoxyvasicinone	R = H	X = O	



Medicinal uses

Uses supported by clinical data

No information was found.

Uses described in pharmacopoeias and well established documents

Used in the treatment of different forms of myasthenia, myopathy and atony of the bowels (*35*).

Uses described in traditional medicine

Used for treatment of epilepsy (*42*), as a central nervous system (CNS)-stimulant, hypnotic and relaxant (*43*, *44*). Also used as an anthelminthic,

diuretic (*45*), diaphoretic, lactogogue (*24*, *46*), aphrodisiac and antiasthmatic (*47*). It is also used as a fumigant for treatment of headache, sore throat and inflammation (*48*), rheumatism (root applied externally) (*49*, *50*), jaundice (*51*), otitis and cataracts (fresh juice and seeds applied locally) (*6*, *52*). Additional described uses of the plant include treatment of dermatitis, alopecia, use as a depurative and abortifacient (*53*), and (fumigation) as a mosquito repellent and pediculocide (*54*).

Pharmacology

Experimental pharmacology

Cardiovascular effects

A methanol extract of the seeds caused a dose-dependent relaxation, after contraction with noradrenaline (10^{-6} M) and potassium chloride (80 mM), in vascular smooth muscle (rat aorta) in vitro at a median inhibitory concentration of 14.49 ± 1.15 and 5.93 ± 1.26 µg/ml, respectively. The vasodilatory effects were potentiated by isoprenaline (10^{-9} M) (1.08 ± 0.14 µg/ml) and decreased by a nonspecific inhibitor of phosphodiesterase 3-isobutyl-1-methylxanthine (10^{-4} M) (20.81 ± 1.06 µg/ml) (*55*).

Cholinergic effects

An aqueous extract of the seeds (0.5 ml) exhibited a smooth muscle relaxant effect in vitro (guinea-pig ileum, rabbit jejunum and trachea) against acetylcholine- and histamine-induced contractions (*56*).

Antinociceptive effects

The analgesic activity of an ethanol extract of the entire dried plant was tested in vivo in mice using the hot-plate test. An intraperitoneal injection of the extract at a dose of 150 mg/kg body weight (bw) demonstrated analgesic effects against acetic acid-induced writhing (*57*).

Hypothermic effect

Intraperitoneal administration of the total alkaloid extract of the aerial parts of the plant to rats (0.5 ml/kg bw) produced significant and dose-dependent hypothermia. Pretreatment with p-chlorophenylalanine (100 mg/kg/day for 3 days), a serotonin (5-hydroxytryptamine, 5-HT) synthesis inhibitor, or with serotonin antagonist methysergide (2 mg/kg), significantly attenuated the hypothermic effect of the total alkaloids. Propranolol (10 mg/kg), a β-adrenoreceptor antagonist, failed to attenuate the effect, suggesting that β-adrenoreceptors are not involved in the pathway producing hypothermia caused by the alkaloids. Pretreatment with a dopamine receptor antagonist, haloperidol (5 mg/kg, subcutane-

ously and 2 mg/kg, intraperitoneally, 24 and 2 h before the experiment, respectively) significantly attenuated the hypothermic effect of harmala alkaloids. Moreover, pretreatment of rats with haloperidol and methysergide (2 mg/kg, intraperitoneally) completely attenuated the hypothermic effect of the alkaloids. Thus, harmala alkaloids produce a hypothermic effect mainly through endogenous stimulation of the 5-HT_{1A} receptor (*58*).

Antimicrobial activity

1-Butanol and aqueous extracts of shade-dried aerial parts (60.0 µg/agar plate) expressed antibacterial activity against *Escherichia coli*. An aqueous extract of the aerial parts was also active against *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Candida albicans* (in broth culture). A methanol extract of dried aerial parts of Herba Pegani harmalae (60 µg/agar plate) was active against *Streptococcus pneumoniae* (*42*) and a 95% ethanol extract of dried entire plant (0.3 mg/ml/agar plate) was active against *Bacillus cereus*, *Staphylococcus aureus* and *Staphylococcus epidermidis* (*59*). Furthermore, an 80% ethanol extract of dried aerial parts demonstrated weak antimycobacterial activity at a concentration of 1 mg/ml/agar plate against *Mycobacterium smegmatis* (*60*).

Anti-inflammatory effects

An ethanol extract of the dried aerial parts and seeds of the plant administered subcutaneously to male rats (100 mg/kg bw) exhibited antiinflammatory effects against carrageenan-induced plantar oedema (58% decrease of inflammation) (*61*).

Antihyperglycaemic effects

Intragastric administration of harmala seed powder at a dose of 53.2 mg/kg bw to rats resulted in an antihyperglycaemic effect. Weight increases were observed in animals with streptozotocin-induced diabetes challenged with glucose after having received a daily dose of extract, 53.2 mg/kg bw, for 1 week (*62*).

Antiparasitic activity

A 100% ethanol extract of dried leaf showed weak in vitro antimalarial activity against *Plasmodium falciparum* with a median inhibitory concentration of 46 µg/ml (*63*). An aqueous extract (concentration 1:200) of the dried leaves of Herba Pegani harmalae exhibited antimalarial activity against *Plasmodium falciparum* FCR-3/Gambia in vitro (*64*).

Uterine stimulant and abortifacient effects
The methanol extract of the aerial parts of the plant at a dose of approximately 2.5 g/kg/day, offered in food or in drinking suspension to female rats for 30 days, significantly prolonged diestrus by 1 day. At doses of 2, 2.5 and 3.5 g/kg/day, the extract appeared to cause a significant dose-dependent decrease in litter size. No change in the physical and nutritional status of the animals and no other adverse toxicological effects were observed (*65*).

Effects on male fertility
Intragastric administration of the dried seeds of Herba Pegani harmalae (100 mg/kg bw) to male rats caused a significant ($p < 0.05$) increase in sperm motility and testosterone level, and augmentation of weight of epididymis, prostate, seminal vesicles and testes (*66*).

Toxicology
The therapeutic and toxic effects in relation to an oral dose of the aqueous extract of Herba Pegani harmalae were studied in Wistar rats. In acute studies, a median lethal dose of 2.70 ± 0.05 g/kg was reported. In chronic studies, oral administration of the extract six times per week at doses of 1, 1.35 and 2 g/kg bw for a 3-month period increased transaminase activity. Histological examination showed liver degeneration and spongiform changes in the central nervous system in rats treated with the 2 g/kg dose, but not in those that received the therapeutic dose of 1 g/kg (*67*). Subcutaneous administration of the 95% ethanol extract (120 mg/kg) of fresh Herba Pegani harmalae to rats, and intraperitoneal administration of the extract to mice (250 mg/kg bw) resulted in toxic effects including stiffness, trembling, frequent urination, hypothermia, weakness, stimulation of the central nervous system, convulsions and death. A median lethal dose of 500 mg/kg was determined from studies of oral administration of the ethanol extract to mice (*68*, *69*). An analysis of 56 medical records of patients admitted to a toxicological intensive care unit from 1983 to 1998 following the ingestion of medicinal plants in Tunisia was performed. The sex ratio of patients (men/women) was 1:2; the mean age of patients was 26 years. A number of plant species were involved; in 7% of the cases *Peganum harmala* was associated with toxicity. Poisoning involved the neurological (91%), gastrointestinal (73%) and cardiovascular systems (18%) (*70*).

Clinical pharmacology
No information was found.

Adverse reactions
No information was found.

Contraindications
The drug is not recommended during pregnancy due to its ability to cause abortion (*59*). Herba Pegani harmalae is contraindicated for paediatric use and for nursing mothers due to its central nervous system exciting effects (*4*, *70*). It is also contraindicated in patients with peptic ulcer (*22*).

Precautions
General
The plant is toxic and should be used with caution (*5*).

Drug interactions
No information was found.

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
A significant increase in the testosterone level in male rats, and a decrease in litter size in female rats has been reported (*65*, *66*).

Pregnancy
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Dosage forms
Comminuted herb for infusion.

Posology
(Unless otherwise indicated)
Internal use. Infusion: one teaspoonful 3–4 times daily. Prepare by placing one teaspoonful of dried herb in 1 cup of boiling water and boiling for 15 minutes on a water bath. Then insist within 2 hours, filter (*8*).

External use. Bath: an infusion from two tablespoonfuls of the cut herb added to 500 ml of water per bath (*6*).

References

1. Comarov VL, Shishkin BK, Bobrov EG, eds. *Flora SSSR. Vol. 14.* Pod red. Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1949.
2. Yakovlev GP, Blinova GF, eds. *Lekarstvennoje rastite'lnoje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
3. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
4. Bown D. *Encyclopedia of herbs & their uses*. London, Dorling Kindersley, 1996.
5. Chevallier A. *The encyclopaedia of medicinal plants*. London, Dorling Kindersley, 1996.
6. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
7. *Standardization of single drugs of Unani medicine*. Part I. New Delhi, Central Council for Research in Unani Medicine (CCRUM), Ministry of Health, Government of India, 1992.
8. Urkunbaev SD et al. *Dikorastushitshie lekarstvenn'e rasteniya K'rg'zstana I ih primenenie*. Uchkun, Bishkek, 2004.
9. Muravjova DA. *Farmakognozija*. Moscow, Meditsina, 1991.
10. Kerbabajev BB. *Narodn'je I nautshn'je Turksmenskije nazvanija rasteni*. Ashabat, 'l'm, 1992.
11. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
12. Kirtikar KR, Basu BD. *Indian medicinal plants.* In 4 vols. Delhi, M/S Bishen Singh Mahendra Pal Singh, 1918.
13. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.
14. Braun R, ed. *Standardzulassungen für Fertigarzneimittel, Stand: Dezember 2004*. Stuttgart, Deutscher Apotheker Verlag, 2005.
15. Nadkarni KM. *Indian materia medica. Vol. 1*. Bombay, Popular Prakashan, 2005.
16. Parsa A. *Flore de l'iran. Vol. VIII*. Tehran, University of Tehran, 1960.
17. Rätsch C. *The encyclopedia of psychoactive plants: Ethnopharmacology and its applications* (Translated by JR Baker). Rochester, VT, Part Street Press, 1998.
18. Chopra RN, Badhwar RL, Ghosh S. Poisonous plants of India. Delhi, Indian Council of Agricultural Research, 1949.
19. Vvedensky AI. *Flora Uzbekistanica. Tomus IV*. Red. Tashkent, Editio Academiae scientiarum UzSSR, 1959.
20. *Eestikeelsete taimenimede andmebaas* [*Index of Estonian plant names*] (http://www.ut.ee/taimenimed/).

21. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
22. Yakovlev GP, Blinova GF, ed. *Rastenija dlja nas.* St Petersburg, Utchebnaja kniga, 1996.
23. Mandaville J. *Flora of Eastern Saudi Arabia*. London, Kegan Paul International, 1990.
24. Batanouny KH. *Wild medicinal plants in Egypt. An inventory to support conservation and sustainable use.* Egypt, Academy of Scientific Research and Technology/Switzerland, International Union for Conservation, 1999.
25. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR.* Izd. Moscow, Mysli, 1976.
26. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR.* 3-ie izd. Kishinev, Shtiintsa, 1986.
27. Shishkin BK. *Botaniceskii atlas* [*Botanical Atlas*], *pod red.* Moscow-Leningrad, Izdatel'stvo sel'skokhoziaistvennoi literatury, jurnalov i plakatov, 1963 [in Russian].
28. *The provisional monograph of USSR pharmacopoiea*. Moscow, 1979 (VFS 42-879-79).
29. Safina LK. *Garmala ob´knovennaya*. Alma-Ata, Izd. Nauka Kazahskoi SSR, 1977.
30. Kartal M, Altun ML, Kurucu S. HPLC method for the analysis of harmol, harmalol, harmine and harmaline in the seeds of *Peganum harmala* L. *Journal of Pharmaceutical and Biomedical Analysis*, 2003, 31:263–269.
31. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
32. *European pharmacopoeia,* 5th ed. Strasbourg, Council of Europe, 2005.
33. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
34. Rastogi RP, Mehrotra BN. *A compendium of Indian medicinal plants. Vol. 4*. New Delhi, Publications & Information Directorate, 1995.
35. Zadorozhnyi AM et al*. Spravotchnik po lekarstvennim rastenijam*. Moscow, Lesnaja promyshlennost', 1988.
36. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Rutaceae-Elaegnaceae. Vol. 4*. Leningrad, Nauka, 1988.
37. Zayed R, Wink M. β-carboline and quinoline alkaloids in root cultures and intact plants of *Peganum harmala. Zeitschrift für Naturforschung, C, Journal of Biosciences*, 2005, 60:451–458.
38. Degtyarev VA, Sadykov YD, Aksenov VS. Alkaloids of *Peganum harmala. Khimiya Prirodnykh Soedinenii*, 1984, 2:255–256.
39. Kurbanov D, Zharekeev B. Alkaloids of *Biebersteinia multifida* and *Peganum harmala* from the Karakalpak ASSR. *Khimiya Prirodnykh Soedinenii*, 1974, 5:685–686.
40. Faskhutdinov MF et al. Alkaloids of *Peganum harmala*. *Chemistry of Natural Compounds*, 2000, 6:602–605.

41. Sharaf M et al. Four flavonoid glycosides from *Peganum harmala. Phytochemistry*, 1997, 3:533–536.
42. Alkofahi A, Masaadeh H, Al-Khalil S. Antimicrobial evaluation of some plant extracts of traditional medicine of Jordan. *Alexandria Journal of Pharmacological Sciences*, 1966, 10:123–126.
43. Dastur JF. *Medicinal plants of India and Pakistan*. Bombay, DB Taraporevala, 1962.
44. Al-Khalil S. A survey of plants used in Jordanian traditional medicine. *International Journal of Pharmacognosy*, 1995, 33:317–323.
45. Rashan LJ, Adaay MH, Al-Khazraji ALT. In vitro antiviral activity of the aqueous extract from the seeds of *Peganum harmala*. *Fitoterapi*a, 1989, 60:365–367.
46. Dragendorff G. *Die Heilpflanzen der verschiedenen Volker und Zeiten* [*The healing plants of various peoples and times*]. Stuttgart, F Enke, 1898.
47. Navchoo IA, Buth GM. Ethnobotany of Ladakh, India: beverages, narcotics, foods. *Economic Botany*, 1990, 44:318–321.
48. Leporatti M, Lattanzi E. Traditional phytotherapy on coastal areas of Makran (Southern Pakistan). *Fitoterapia*, 1994, 65:158–161.
49. Shah NC. Herbal folk medicines in Northern India. *Journal of Ethnopharmacology*, 1982, 6:293–301.
50. Singh V, Kapahi BK, Srivastava TN. Medicinal herbs of Ladakh especially used in home remedies. *Fitoterapia*, 1996, 67:38–48.
51. Schipper A, Volk O. The alkaloids of *Peganum Harmala*. *Deutsche Apotheker Zeitung*, 1960, 100:255.
52. Bellakhdar J et al. Repertory of standard herbal drugs in the Moroccan Pharmacopoeia. *Journal of Ethnopharmacology*, 1991, 35:123–143.
53. Amirdowlat Amasyaci. *Nenuzhnoe dlja neuczej* [*Needless for ignoramus*]. Naucznoe nasledstvo. Moscow, Nauka, 1990.
54. Nayar SL. Vegetable insecticides. *Bulletin of National Institute of Sciences of India*, 1955, 4:137–145.
55. Berrougui H et al. Relaxant activity of methanolic extract from seeds of *Peganum harmala* on isolated rat aorta. *Therapie*, 2002, 57:236–241.
56. Aqel M, Hadidi M. Direct relaxant effect of *Peganum harmala* seed extract on smooth muscles of rabbit and guinea pig. *International Journal of Pharmacognosy*, 1991, 29:176–182.
57. Twaij HA, Elisha EE, Khalid RM. Analgesic studies on some Iraqi medicinal plants part II. *International Journal of Crude Drug Research*, 1989, 27:109–112.
58. Abdel-Fattah et al. Hypothermic effect of harmala alkaloid in rats: involvement of serotonergic mechanism. *Pharmacology*, *Biochemistry and Behavior*, 1995, 52:421–426.
59. Hussain H, Tobji RS. Antibacterial screening of some Libyan medicinal plants. *Fitoterapia*, 1997, 68:467–470.

60. Al-Shamma A, Mitscher LA. Comprehensive survey of indigenous Iraqi plants for potential economic value. I. Screening results of 327 species for alkaloids and antimicrobial agents. *Journal of Natural Products*, 1979, 42:633–642.
61. Benoit PS et al. Biological and phytochemical evaluation of plants. XIV. Anti-inflammatory evaluation of 163 species of plants. *Lloydia*, 1976, 39:160–171.
62. Al-Zaid MM et al. Evaluation of blood glucose lowering activity of three plant diet additives. *International Journal of Pharmacognosy*, 1991, 29:81–88.
63. Simonsen HT et al. *In vitro* screening of Indian medicinal plants for anti-plasmodial activity. *Journal of Ethnopharmacology*, 2001, 74:195–204.
64. Sathiyamoorthy P et al. Screening for cytotoxic and antimalarial activities in desert plants of the Negev and Bedouin market plant products. *Pharmaceutical Biology*, 1999, 37:188–195.
65. Shapira Z et al. Abortifacient potential for the epigeal parts of *Peganum harmala*. *Journal of Ethnopharmacology*, 1989, 27:319–325.
66. Subhan F et al. Aphrodisiac potential of *Peganum harmala* seeds. *Hamdard-Medicus*, 1998, 41:69–72.
67. Lamchouri F et al. Experimental toxicity of *Peganum harmala* seeds. *Annales Pharmaceutiques Francaises*, 2002, 60:123–129.
68. Woo WS et al. Biological evaluation of some Saudi Arabian plants. *Journal of Pharmaceutical Society of Korea*, 1977, 21:141.
69. El-Bahri L, Chemli R. *Peganum harmala* L: a poisonous plant of North Africa. *Veterinary and Human Toxicology*, 1991, 33:276–277.
70. Hamouda C et al. Plant poisonings from herbal medication admitted to a Tunisian toxicologic intensive care unit, 1983-1998. *Veterinary and Human Toxicology*, 2000, 42:137–141.

Folium Plantaginis majoris

Definition

Folium Plantaginis majoris consists of the whole or cut dried leaves of perennial *Plantago major* L. (Plantaginaceae) collected during the flowering season from both cultivated and wild plants (*1*).

Synonyms

Plantago asiatica L., *P. borysthenica* (Rogow.) Wissjul., *P. bracteata* Moench, *P. dostalii* Domin, *P. halophila* E.P. Bicknell, *P. intermedia* DC., *P. limosa* Kit. ex Schult., *P. minimia* DC in Lam. & DC., *P. nana* Tratt., *P. nitrophila* A. Nelson, *P. officinarum* Crantz, *P. paludosa* Turcz. ex Ledeb., *P. pauciflora* Domin, *P. pumila* Krock., *P. scopulorum* Pavlova, *P. sorokini* Bunge, *P. uliginosa* F.W. Schmidt in E. Mayer, *P. vulgaris* Pavlova (2–4).

Selected vernacular names

Arnoglossa, bağ yapraği, baka zhal by rak, bartang, bazir dam bil, breitwegerich, broadleaf plantain, broad-leaved plantain, büyük sinirliot, büyük sinir out, cart-track plant, celtekas, ceuli, ceuli uncal, chajeoncho, ch'e ch'ien, che qian zi, common plantain, cuckoo's bread, damarotu, daum sejumbok, daun sendok, daun urat, door-yard plantain, ekur anjing, ezan lezu, gechi oulaghi, Englishman's foot, filo, filomatolu, grand plantain, grant plantain, great plantain, greater plantain, grosser Wegerich, grote weegbree, healing-blade, henplant, jghakhot, katir, katta zubturum, kesirotu, ki urat, kuping menjangan, lahuriya, lanting, lanting haba, lamb's-foot, laukahi, lielā ceļmalīe, lisan al-hamal, llantén, llantén común, llanten mayor, llanten, meloh kiloh, mo noi, nipple grass, otot ototan, pătlagină, piantaggine grande, piantaggine maggiore, piharatamo, phak kat nam, plantain, plantain commun, plantain majeur, plantate gros, podorozhnik bolshoi, poputnik, pridorozhnik, priputnik, putiki, putnik, ratamo, ribgrass, ripple grass, sangka buwah, sangkubah, sangkuwah, sei ohr re, sembung otot, sinurotu, snakeweed, sobatshi jazyk, suri pandak, suur teeleht, tanagem, tanchagem-maior, tarkuz, tirnagt, torongoat, triputnik, tsirevaja trava, twissat mariam, wayboard, waybread, wegerlich, white-man's foot (3, *5–24*).

Geographical distribution

Indigenous to the temperate regions of the world (especially Asia and Europe). Naturalized elsewhere in temperate regions. It is found in the Mediterranean and Western Asia. Rarely cultivated, it is normally harvested from the wild (*3*, *5*, *6*, *25–29*).

Description

Perennial herb, with scapes, up to 30 cm high, short rhizome, fibrous primarily adventitious roots. Caudex short. Basal rosette-like leaves broadly elliptic to ovate, obtuse to rounded at the top, entire or irregularly toothed, strongly parallel-veined (3–9 ribs, usually 5), tapered into long petioles, 4–24 cm long, 2.5–11 cm wide, pubescent when young, remaining pubescent on the principal veins or becoming glabrous at maturity. Stem leaves lacking. Inflorescence of dense, narrow, bracteate spikes. Spikes less than 1 cm thick, 5–30 cm long, green-brown, smooth. Flowers hermaphrodite, anemophilous and/or autogamous. Peduncle glabrous. Bracts concave, ovate-oblong, obtuse, thin-margined, 1.5–4 mm long. Calyx 3 mm long, sepals subequal, distinct, ovate to suborbicular, 2–2.5 mm long, glabrous. Corolla greenish, 4-lobed, the lobes deltoid, less than 1 mm long. Stamens inconspicuous, filaments white, anthers violet to yellowish-brown. Capsules, ovate, 2.5–4 mm long, glabrous, dehiscent at or slightly below middle, the top coming off as a conical lid tipped with the remains of the style. Seeds 5–25, black or brown, 1 mm long, finely veined (*6*, *8*, *27*, *28*, *30*, *31*).

Plant material of interest: dried leaves

General appearance

Dried, whole or partly fragmented twisted leaves. The dried leaves are ovate or broadly elliptic, entire or toothed, 3–9 ribbed. The ribs taper into a long petiole and they protrude from the cut edge. The leaves are green or brownish-green, up to 24 cm long (including the length of petiole) and 3–11 cm wide. The fragments of cut drug are irregular; their dimensions (length and width) vary within a 7 mm limit (*1*).

Organoleptic properties

Odour: slight; taste: slightly bitter (*1*).

Microscopic characteristics

Examining the surface of the leaf, two epidermises can be distinguished: an upper epidermis (polygonal cells with straight cell walls) and a lower

epidermis (polygonal cells with slightly sinuous cell walls). There are anomocytic stomata on both epidermises, but mainly on the lower one. The epidermal cells occasionally have a striated cuticle. There are rosettes of epidermal cells with attached or detached trichomes of two types: simple and glandular. The simple trichomes are multicellular, smooth, with an enlarged base. The glandular trichomes have a monocellular stalk and a bicellular elongated head, rarely a multicellular stalk and an oval or spherical unicellular head. The length of trichomes varies between 30 and 200 µm (*1*, *27*, *32*). In transverse section, there are tannins in the mesophyll cells (*33*).

Powdered plant material

Green or brownish-green. The powder has the same microscopic characteristics as the whole leaf (see Microscopic characteristics). The trichomes may be broken off at the "joints".

General identity tests

Macroscopic and microscopic examinations. Phytochemical reactions for detection of polysaccharides and galacturonic acid (*1*). Thin-layer chromatography for detection of aucubin. Visualization reagents: phloroglucinol and hydrochloric acid (*32*), dimethyl benzaldehyde (*34*), benzidine or anisaldehyde or vanillin-sulfuric acid reagents (*35*). The specific iridoids can be valuable taxonomic markers (*36*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*37*).

Chemical

No information available.

Foreign organic matter

Not more than 1% of foreign organic matter. Not more than 5% of brownish and blackish leaves. Not more than 1% of inflorescences. Not more than 5% of fragments of drug having a diameter less than 1 mm. For cut drug: not more than 10% of fragments having a diameter more than 7 mm; not more than 7% of fragments having a diameter less than 0.5 mm (*1*).

Total ash
Not more than 20% (*1*) or not more than 15% (*38*).

Acid-insoluble ash
Ash insoluble in 10% hydrochloric acid not more than 6% (*1*).

Sulfated ash
No information available.

Water-soluble extractive
Not less than 30% (*27*).

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 14% (*1*).

Pesticide residues
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*39*). For other pesticides, see the *European pharmacopoeia* (*39*) and the WHO guidelines on quality control methods for medicinal plant materials (*37*) and pesticide residues (*40*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*37*).

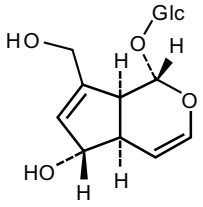
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*37*) for the analysis of radioactive isotopes.

Other purity tests
The content of mineral matter not more than 1% (*1*). Chemical, sulfated ash and alcohol-soluble extractive tests are to be established in accordance with national requirements.

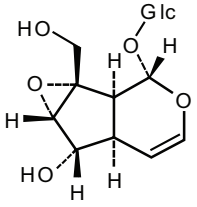
Chemical assays
Contains not less than 12% polysaccharides (*1*).

Major chemical constituents

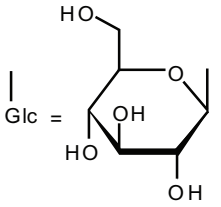
Dried leaves contain iridoids as the main constituents: aucubin, 3,4-dihydroaucubin, 6´-*O*-β–glucosylaucubin, catalpol, plantarenaloside and melittoside. Also mucilage (up to 12%); flavonoids (apigenin, baicalein, scutellarein, baicalin, homoplantaginin, nepetrin, luteolin, hispidulin, plantagoside); carbohydrates (L-fructose, D-glucose, planteose, saccharose, stachyose, D-xylose, sorbitol, tyrosol, mucilage and gum); alkaloids (boschniakine, methyl ester of boschniakinic acid); acids (benzoic, caffeic, chlorogenic, cinnamic, *p*-coumaric, ferulic, fumaric, gentisic, 4-hydroxybenzoic, neochlorogenic, salicylic, syringic, ursolic, vanillic and oleanolic); amino acids; lipids; proteolytic enzymes; tannins (approximately 4%), saponins; steroids; and vitamins are present (*18*, *22*, *27*, *29*, *41–47, 91*). The carbohydrate component of the plantaglucide polysaccharide isolated from leaves of *P. major* consists of galacturonic acid (27%) and monosaccharides: galactose, glucose, mannose, xylose, arabinose and fucose (*48*). The structures of some characteristic constituents are presented below.



aucubin



catalpol



β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

No information was found.

Uses described in pharmacopoeias and well established documents

Plantago major is used internally for catarrh of the respiratory tract, cough, bronchitis, inflammatory alterations of the oral mucosa, phlegm congestion, nephritis, cystitis, urinary retention, dysentery, epistaxis (nosebleed) and excessive diaphoresis (*49*, *50*). It is also used for the treatment of diarrhoea and constipation (*22*).

Uses described in traditional medicine

Fresh leaves of *Plantago major* have been used externally for centuries in many parts of the world as an antiseptic for treatment of skin irritations, erysipelas, abscesses, burns, scrofula and inflammatory reactions of the

skin; for repair of damaged tissue; and to treat fistulae and ulcers (*5*, *43*, *51*, *52*). It is also used to suppress cough associated with bronchitis, colds and upper respiratory inflammation, and as an analgesic and diuretic agent, in the treatment of kidney stones (*53–55*). It also has a hepatoprotective action (*4*, *56*). *Plantago major* leaves have been used as a weak antibiotic, astringent (*57*) and as an immunomodulating (*58*), antihypertensive (*59*), hypoglycaemic (*60*), haemostatic (*61*), antiallergic, febrifuge and antipruritic agent (*62*). It is used in the treatment of eye inflammation, and as a vermifuge (*63–65*). It is commonly prescribed for treatment of cystitis with haematuria and haemorrhoids (*38*).

Pharmacology

Experimental pharmacology

Antiviral, cytotoxic and immunomodulatory activities

The antiviral activity of an aqueous extract and pure components of *P. major* leaves against herpes viruses (HSV-1 and HSV-2) and adenoviruses (ADV-3, ADV-8 and ADV-11) was studied in vitro. The median effective concentration (EC_{50}) for antiviral activity was defined as the concentration that achieved 50% cytoprotection against virus infection. The selectivity index was determined by the ratio of the EC_{50}s for cytotoxicity and cytoprotection, as defined above. The results showed that the extract had low sensitivity for herpes virus (*66*).

The antiviral, cytotoxic and immunomodulatory activities of a hot-water extract of the leaves was investigated in vitro against a series of viruses, namely herpes viruses (HSV-1 and HSV-2), adenoviruses (ADV-3, ADV-8 and ADV-11), and in various human leukaemia, lymphoma and carcinoma cells. The activity was measured using XTT, BrdU and interferon-gamma kits. The results demonstrated that the extract possessed significant inhibitory activity against the proliferation of lymphoma (U937) and carcinoma (bladder, bone, cervix, kidney, lung and stomach) cells and against viral infection (HSV-2 and ADV-11). The extract exhibited both immunostimulant and immunosuppressive activities; at low concentrations (< 50 µg/ml), it enhanced lymphocyte proliferation and secretion of gamma-interferon; however, at a high concentration (> 50 µg/ml), it inhibited these effects. It was concluded that the extract possesses a broad spectrum of antileukaemia, anticarcinoma and antiviral activities, as well as activities which modulate cell-mediated immunity. Immunomodulatory activity of a decoction of dried leaves of *P. major* was observed in vitro using the lymphocyte transformation test and stimulation of gamma-interferon production (at concentrations of 12.5 µg/ml and 25 µg/ml, respectively) (*67*).

Studies using individual components of the *P. major* leaf extracts were conducted on lymphocyte transformation by the BrdU immunoassay. Also studies of secretion of gamma-interferon using an enzyme-linked immunosorbent assay (ELISA) were performed. The results showed that the water-soluble components, namely aucubin, chlorogenic acid, ferulic acid, *p*-coumaric acid and vanillic acid, enhanced the activity of human lymphocyte proliferation and secretion of gamma-interferon. Among the water-insoluble components, with the exception of luteolin, both baicalein and baicalin resulted in an enhancement of the human peripheral blood mononuclear cells. Although oleanolic acid and ursolic acids did not significantly affect the proliferation of peripheral blood mononuclear cells they exhibited a strong stimulation of gamma-interferon secretion. Linalool, a monoterpenoid, showed immunomodulatory activity similar to that of the triterpenes (*46*).

An endotoxin-free methanol extract from *P. major* leaves, at doses of 50, 100, 250 and 500 µg/ml, increased nitric oxide production by 4.4 ± 1, 6 ± 1, 12 ± 0.4 and 18 ± 0.4-fold, and increased tumour necrosis factor alpha (TNFα) production by 621 ± 31, 721 ± 36, 727 ± 36 and 1056 ± 52 U/ml, respectively in rat peritoneal macrophages. Nitric oxide and TNFα production in untreated macrophages was negligible. In addition, the extract dose-dependently potentiated concanavalin A-induced lymphoproliferation (3- to 12-fold increases), as compared with concanavalin A alone. The regulation of immune parameters induced by the plant extract may be clinically relevant in numerous diseases (*68*).

Haematopoietic effects

Aqueous, methanol, chloroform and hexane extracts of *P. major* leaves were tested for immunostimulant and haematopoietic activities (independent and interdependent) on cultures of *Escherichia coli*, *Bacillus subtilis* and *Candida albicans* and also on CD(1) mice bone marrow and splenocyte cultures (37 °C for 72 hours). Aqueous and methanol extracts at concentrations of 0.4 and 0.2 mg/ml increased the bone marrow cell concentration by 2.70-fold and 3.15-fold, and also increased the spleen cell concentration by 3.38-fold and 6.39-fold, respectively ($p < 0.001$). The data demonstrated in vitro haematopoietic activity of *P. major* (*69*).

Antimicrobial activity

A 50% aqueous-ethanol extract of dried leaves of *P. major* had antibacterial activity against *Shigella dysenteriae* at a concentration of 50 µl/agar plate (*70*) in vitro. A tincture (1:10) was active against *Bacillus subtilis* (0.1 ml/agar plate), *Escherichia coli* (30 µl/disc), and *Staphylococcus aureus*

(30 µl/disc) (*52*). An ointment from *P. major* leaves expressed antiyeast activity against *Candida albicans* at a dose of 20.7 µg/g/agar plate (*71*). The antibacterial effect of a pectin polysaccharide isolated from *P. major* leaves was examined in inbred NIH/OlaHsd and Fox Chase SCID mice, infected with *Streptococcus pneumoniae* serotype 6B. The pectin polysaccharide was administered intraperitoneally (12 µg/animal) either once, three days before challenge, or one to three times, 3–48 hours after challenge. The number of bacteria in blood and the mouse survival rates were recorded. Pre-challenge administration of the polysaccharide and also a lipopolysaccharide (included as a control), provided a dose-dependent protective effect against *S. pneumoniae* serotype 6B infection. However, injection of pectic polysaccharide after establishment of the infection in mice had no effect. These results demonstrate that the pectic polysaccharide fraction from *P. major* protects against pneumococcal infection in mice when administered systemically before challenge, and that the protective effect is due to stimulation of the immune system (*72*).

Antiparasite activity

Weak antigiardiasis activity of a decoction of *Plantago* leaves at a concentration of 60 mg/ml, was observed in vitro in a blinded study using trophozoites of *Giardia duodenalis* incubated with the decoction. The viability of trophozoites was determined using 3-[4,5-dimethylthiazol-2-il]-2,5-diphenyl tetrazolium bromide (MTT), which is reduced to MTT-formazan by the activity of live trophozoites. The reduced MTT was extracted and measured by spectrophotometry at 570 nm. Negative (trophozoites without extract) and positive controls (incubated with tinidazol) were also analysed. Antigiardiasis activity of the decoction as determined by trophozoite mortality was 76 ± 1.2% (*73*).

Antinociceptive effects

The antinociceptive effect of methanolic extracts of *P. major* leaves (400 g/kg body weight (bw)) was studied in mice using the acetic acid-induced writhing inhibition and tail-flick tests. Orally administered extract inhibited the nociception to acetic acid-induced writhing with a protection of 50.8–45.8% compared with controls. In the tail-flick test, at a dose of 400 mg/kg bw, the extract significantly increased the latency in response of the tail to thermal stimulation. At doses up to 2 g/kg bw, the extracts did not cause any deaths or major signs of acute toxicity (*74*). Intragastric administration of an aqueous extract of dried leaves of *P. major* inhibited acetic acid-induced writhing in mice at a dose of 1 g/kg bw (*65*).

Anti-inflammatory activity

The intragastric administration of an aqueous extract of dried leaves of *P. major* at a dose of 1 g/kg bw inhibited carrageenan-induced pleurisy and plantar oedema in rats. A doubling of the dose of the extract (to 2 g/kg bw) inhibited development of croton oil-induced granuloma (*65*). Ursolic and oleanolic acids were isolated from a hexane extract of dried leaves using bioactivity-directed fractionation. Both substances had anti-inflammatory activity (*75*).

Histamine release inhibiting activity

An ethanol extract of *P. major* leaves was tested for its ability to inhibit histamine release from RBL-2H3 cells (rat basophilic leukaemia cell line), a tumour analogue of mast cells. The ethanol extract (0.5 mg/ml) inhibited immunoglobulin E-dependent histamine release from RBL-2H3 cells. The inhibitory effect was greater than 80%. The results indicate that the active components of this extract inhibiting mast cell degranulation could be useful in the treatment of asthma (*76*).

Diuretic activity

Intragastric administration of a decoction of *P. major* leaves to rats, at a dose of 1 g/kg bw, stimulated diuresis (*55*).

Antitumour effects

A 70% ethanol extract and an aqueous-ethanol (1:1) extract of dried leaves demonstrated anticrustacean activity in the *Artemia salina* assay at a median lethal concentration of 7 µg/ml and a median inhibitory concentration of 4.74 µg/ml, respectively. The ethanol extract also inhibited β-glucuronidase activity at a median inhibitory concentration of 17 µg/ml (*77*). Fifty-two per cent inhibition of sarcoma 180 (ASC) cell growth was detected in vivo in mice after intraperitoneal injection of 0.2 mg/kg of a 95% ethanol extract for 5 days (*78*). In a chronic experiment in rats, administration of a polyphenolic complex from *P. major* leaves – plantastine (the route of administration was not mentioned) decreased the effect of an endogenously synthesized carcinogen, nitroso-diethylamine. This carcinogenic compound is synthesized in rats following the long-term administration of amidopyrine and sodium nitrite causing toxic damage to the liver and production of tumours. The number of neoplasms was 33.3% in animals receiving plantastine and 87.5% in rats given the amidopyrine/sodium nitrite combination. Plantastine also decreased the normal level of enzyme activity induced by amidopyrine and sodium nitrite (*79*). A methanol extract from air-dried and powdered *Plantago* leaves was evalu-

ated for cytotoxic activity against the human cancer cell lines: human renal adenocarcinoma (TK-10), human breast adenocarcinoma (MCF-7) and human melanoma (UACC-62). The sulforhodamine B assay was used in this study to assess growth inhibition. The concentrations of extract (µg/ml) required to inhibit cell growth by 50% were: > 250 (TK-10); 46.5 ± 7.1 (MCF-7) and 46.5 ± 8.2 (UACC-62). The concentrations required to produce total growth inhibition were: > 250 (TK-10); 97.5 ± 1.8 (MCF-7) and 112.5 ± 2.1 (UACC-62), and the concentrations required to cause 50% net cell death were: > 250 (TK-10); 207 ± 18.20 (MCF-7) and 247 ± 12.3 (UACC-62). The results demonstrate that the extract has weak cytotoxic activity with a certain degree of selectivity against the tested cells in culture. The results could justify the traditional use of *P. major* as an antitumour agent (*80*).

Wound-healing activity

The dermal application of the non-hydrolysable chromatographic fraction (10%) from the hexane extract (25%) of dried leaves of *P. major* significantly ($p < 0.001$) accelerated the rate of contraction and epithelialization of excision wounds in rabbits (*81*).

The interaction between a pectin-type polysaccharide fraction (PTPF), isolated from the leaves of *P. major*, and human complement was tested in vitro using two different haemolytic complement-fixation tests and two ELISA methods for detection of complement-activation products. Serum from 10 human volunteers was used as a complement source. The complement-fixation tests were designed to measure the concentration of the pectin necessary to inhibit haemolysis by 50% (ICH_{50}). The ELISA tests, for determination of complement-activation products, utilized a fully activated serum as a standard. A greater than 200-fold difference in ICH_{50} activity of the PTPF pectin was observed in one of the haemolytic tests when the individual serum used as the complement-source was varied. By contrast, the ELISA complement-activation tests showed no significant variation in activity of the PTPF in relation to the complement serum used. The level of antibodies against PTPF detected in the complement sera did not correlate with the ICH_{50} activity of PTPF. The results indicate that PTPF is a potent complement activator with an activity of the same order of magnitude as that of aggregated human immunoglobulin G. The results might be related to the wound-healing effect of the leaves of *P. major* (*82*).

Toxicology

The median lethal dose (LD_{50}) for intragastric administration of an aqueous-ethanol (1:1) extract of *P. major* leaves to mice was determined to be

11.9 g/kg (*77*, *83*). The somatic mutation and recombination test in *Drosophila melanogaster* was used to evaluate the genotoxic activity of an aqueous extract of *P. major* leaves. Two *Drosophila* crosses were produced: a standard cross and a high-bioactivation cross. Each cross produced two types of descendents. Three-day-old larvae of both types of descendents were treated with undiluted and diluted extract (1:1 and 1:2 in water). The extracts were genotoxic in both crosses, the number of induced frequencies produced were similar in both types of flies. Comparison of the frequencies of wing spots in the descendents indicated that recombination was a major response. The results indicate that, under these experimental conditions, aqueous extracts are genotoxic (recombinogenic) (*84*). Subchronic toxicity of an aqueous preparation of leaves was tested in 20 NGP male mice, with an average weight of 20.1 g. The extract (2000 mg/kg) was administered once daily on 5 days a week for a total of 40 days. The control group received 0.5 ml of distilled water instead of extract. Signs of subchronic toxicity were recorded on days 2 and 12 of treatment. No significant changes in body weight were observed in mice that received the aqueous extract and control mice. Ocular irritation was tested for in five male New Zealand rabbits, with an average weight of 3.6 kg. The dose used was 200 µl of a preparation (100 mg/ml) of *Plantago major* leaves, instilled into the conjunctiva. The extract caused no significant irritation during the observation period (*85*). A saline extract of dried leaves of *P. major* was studied for potential genotoxicity in the *Salmonella typhimurium* microsomal activation assay and the alkaline single-cell gel electrophoresis (COMET) assay. The extract (40 µg/agar plate) did not cause a positive response in strains TA98 or TA100 of *Salmonella typhimurium* with or without metabolic activation, but increased values above those of the negative control in the COMET assay. The results indicate that the extract has genotoxic activity in human lymphocytes (*86*).

Clinical pharmacology

No information was found.

Adverse reactions

Allergic contact dermatitis in response to *P. major* has been reported (*87*).

Contraindications

In case of hypersensitivity to *P. major* pollen (e.g. contact dermatitis), use should be stopped.

Warnings
No information was found.

Precautions

General
No information was found.

Drug interactions
No information was found.

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found on carcinogenesis or impairment of fertility. Genotoxic activity of the aqueous-ethanolic and saline extracts has been reported under experimental conditions (see Toxicology above).

Pregnancy
The use of the herb is not recommended during pregnancy (see sections on Toxicology and Genotoxicity).

Nursing mothers
No information was found.

Paediatric use
No information was found.

Dosage forms
Comminuted herb used for infusions and other Galenical preparations for internal use. Juice of the leaves of *Plantago major* (*89*).

Posology
(Unless otherwise indicated)
Internal. Granules of dried leaf: 2–4 g three times daily, before meals (*38*). Infusion: one tablespoon of an infusion (10 g dried leaf in 200 ml boiled water for 15–20 minutes) three times daily before meals (*89*). Liquid extract: 2–4 ml of a liquid extract from dried leaf (1:1 in 25% ethanol) three

times daily (*41*). Tincture: 2–4 ml of a tincture of dried leaf (1:5 in 45% ethanol) three times daily (*41*). Juice of the fresh leaves: one tablespoon three times daily, before meals (*28*).
External. Cold macerate for use as a rinse, gargle or cataplasm: soak 1.4 g cut herb in 150 ml cold water for 1–2 hours, stirring often. For use as a rinse or gargle: rinse or gargle with cold macerate (soak 1.4 g cut herb in 150 ml cold water for 1–2 hours stirring often) three to four times daily (*90*).

References

1. *USSR Pharmacopoeia*. 11th ed. Vol 2. Moscow, Meditsina, 1990.
2. *Armenian national formulary for herbal medicines*. Yerevan, Drug and Medical Technology Agency Ministry of Health of RA JSC, 2001.
3. *Northern Ontario plant database* (http://www.northernontarioflora.ca/).
4. *Hager-ROM*. *Plantago major* Blätter (Breitwegerichblätter) [*Plantago major* leaves (Breitwegerichblätter)]. Heidelberg, Springer Verlag, 2003 [in German].
5. Chevallier A. *The encyclopedia of medicinal plants*. London, Dorling Kindersley, 1996.
6. Boulous L, El-Hadidi MN. *The weed flora of Egypt.* Revised ed. Cairo, American University in Cairo, 1994.
7. Nadkarni AK. *Indian materia medica.* Vol. 1. Mumbai, Popular Prakashan Private Press, 1992.
8. *Homoeopathic Pharmacopoeia of India.* Vol. 2. Delhi, Government of India, Ministry of Health, 1974.
9. Petkov V, ed. *Sovremennaja fitoterapija.* Sofia, Meditsina i fizkultura, 1988.
10. Urkunbaev ShD, Nuralieva ZhS, Alimbaeva PK, Chaldanbaeva AK. *Dikorastushitshie lekarstvenn'e rasteniya K'rg'zstana I ih primenenie* [Wild medicinal plants of Kyrgyzstan and their application]. Bishkek, Uchkun, 2004 [in Russian].
11. Turova AD, Sapozhnikova EN. *Lekarstvennie rastenija SSSR i ikh primenenie*. Moscow, Meditsina, 1982.
12. *Plantain* Plantago major *use. Alternative nature online* (http://altnature.com/gallery/plantain.htm).
13. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
14. Īriste V, Eniņa V. *Ārstniecības augu vārdnīca.* Riga, Medikamentu informācijas centers, 2000.
15. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
16. De Padua LS et al., eds. Medicinal and poisonous plants 1. *Plant resources of South-East Asia*, 1999, 12:194.
17. *Materia medika Indonesia.* Vol. 1. Jakarta, Departemen Kesehatan Republik Indonesia, 1977.

18. Kim IH et al. *Medicinal botany*. Seoul, Hakchang, 2003.
19. Grigorescu E, Ciulei I, Ursula S. *Index fitoterapeutic.* Bucharest, Editura Medicala, 1986.
20. Yazicioglu A, Tuzlaci E. Folk medicinal plants of Trabzon (Turkey). *Fitoterapia,* 1996, 4:307–318.
21. Merzouki A et al. Wild medicinal plants used by local Bouhmed population (Morocco). *Fitoterapia,* 1997, 5:444–460.
22. Blumenthal M, Goldberg A, Brinckmann J., eds. *Herbal medicine, expanded Commission E monographs.* Austin, TX, American Botanical Council, 2000.
23. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
24. Bedevian AK. *Illustrated polyglottic dictionary of plant names*. Cairo, Medbouly Library, 1994.
25. Plantago major (PIER species info) (http://www.hear.org/pier/species/plantago_major.htm).
26. Muravjova DA. *Farmakognozija*. Moscow, Meditsina, 1991.
27. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
28. Yakovlev GP, Blinova KF, ed. *Rastenija dlja nas.* St. Petersburg, Utchebnaja kniga, 1996.
29. Yakovlev GP, Blinova KF, ed. *Lekarstvennoje rastitel'noje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
30. Kirtikar KR, Basu BD, I.C.S. A. *Indian medicinal plants.* In 4 vols. Delhi, M/S Bishen Singh Mahendra Pal Singh, 1918.
31. *Standardization of single drugs of Unani medicine.* Part II. Central Council for Research in Unani Medicine (CCRUM), New Delhi, Ministry of Health, Government of India, 1992.
32. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants,* 2nd ed. Paris, Intercept, 1999.
33. Toma C, Rugina R. *Anatomia plantelor medicinale. Atlas*. Bucharest, Ed. Academiei Românei, 1998.
34. Wichtl M, ed. *Teedrogen und Phytopharmaka*. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 2002.
35. Wagner H, Bladt S, Zgainski EM. *Plant drug analysis.* Berlin, Springer, 1984.
36. Ronsted N et al. Chemotaxonomy of *Plantago*. Iridoid glucosides and caffeoyl phenylethanoid glycosides. *Phytochemistry*, 2000, 55:337–348.
37. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
38. *British herbal pharmacopoeia*. Vol. 1. Keighley, British Herbal Medicine Association, 1983.
39. *European pharmacopoeia*, 5th ed. Strasbourg, Council of Europe, 2005.
40. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).

41. Barnes J, Anderson LA, Philipson JD. *Herbal medicines: A guide for healthcare professionals,* 2nd ed. London, Pharmaceutical Press, 2002.
42. Maksyutina IP. Polyphenol compounds of *Plantago major* leaves. *Farmatsevtichnii Zhurnal,* 1972, 27:59–63.
43. Samuelsen AB. The traditional uses, chemical constituents, and biological activities of *Plantago major*. A review. *Journal of Ethnopharmacology*, 2000, 71:1–21.
44. Istudor V. *Farmacognozie, fitochimie, fitoterapie* [*Pharmacognosy, phytochemistry, phytotherapy*]. Bucharest, Editura Medicala, 1998.
45. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Caprifoliaceae-Plantaginaceae.* Vol. 5. Leningrad, Nauka, 1990.
46. Chiang LC et al. Immunomodulatory activities of flavonoids, monoterpenoids, triterpenoids, iridoid glycosides and phenolic compounds of *Plantago* species. *Planta Medica*, 2003, 69:600–604.
47. Nishibe S, Murai M. Bioactive components of Plantago herb. *Food & Food Ingredients Journal of Japan*, 1995, 166:43–49.
48. Dzyuba NP, Chushenko VN. Determination of the qualitative and quantitative composition of polysaccharides in plant raw material and preparations by physicochemical methods. Communication II. *Farmatsevtichnii Zhurnal,* 1977, 32:56–59.
49. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
50. *Selected medicinal plants in Viet Nam*. Manila, WHO Regional Publications, Western Pacific Series, 1999.
51. Hussey JS. Some useful plants of early New England. *Economic Botany*, 1974, 28:311.
52. Caceres A et al. Screening of antimicrobial activity of plants popularly used in Guatemala for the treatment of dermatomucosal diseases. *Journal of Ethnopharmacology*, 1987, 20:223–237.
53. Gupta MP et al. Ethnopharmacognostic observations on Panamanian medicinal plants. Part I.Q. *Journal of Crude Drug Research*, 1979, 17:115–130.
54. Anderson EF. Ethnobotany of hill tribes of northern Thailand. II. Lahu medicinal plants. *Economic Botany*, 1986, 40:442–450.
55. Caceres A, Giron LM, Martinez AM. Diuretic activity of plants used for the treatment of urinary ailments in Guatemala. *Journal of Ethnopharmacology*, 1987, 19:233–245.
56. De Feo V, Senatore F. Medicinal plants and phytotherapy in the Amalfitan coast, Salerno province, Campania, Southern Italy. *Journal of Ethnopharmacology,* 1993, 39:39–51.
57. Al-Khalil S. A survey of plants used in Jordanian traditional medicine. *International Journal of Pharmacognosy*, 1995, 33:317–323.
58. Brandao M, Botelho M, Krettli E. Antimalarial experimental chemotherapy using natural products. *Ciência e Cultura*, 1985, 37:1152–1163.

59. Nagata KM. Hawaiian medicinal plants. *Economic Botany*, 1971, 25:245.
60. Rodriguez J et al. Hypoglycaemic activity of *geranium core-core, oxalis rosea* and *Plantago major* extracts in rats. *Phytotherapy Research*, 1994, 8:372–374.
61. Srivastava RC. High altitude medicinal plants of Sikkim Himalaya. *Journal of Research in Indian Medicine*, 1993, 12:5–14.
62. Basaran AA et al. Immunomodulatory activities of some Turkish medicinal plants. *Phytotherapy Research*, 1997, 11:609–611.
63. Logan MH. Digestive disorders and plant medicine in highland Guatemala. *Anthropos*, 1973, 68:537–543.
64. Novaretti R, Lemordant D. Plants in the traditional medicine of the Ubaye valley. *Journal of Ethnopharmacology*, 1990, 30:1–34.
65. Guillen ME et al. Analgesic and antiinflammatory activities of the aqueous extract of *Plantago major* L. *International Journal of Pharmacognosy*, 1997, 2:99–104.
66. Chiang LC et al. Antiviral activity of *Plantago major* extracts and related compounds *in vitro*. *Antiviral Research*, 2002, 55:53–62.
67. Chiang LC et al. In vitro cytotoxic, antiviral and immunomodulatory effects of *Plantago major* and *Plantago asiatica*. *American Journal of Chinese Medicine*, 2003, 31:225–234.
68. Gomez-Flores R et al. Immunoenhancing properties of *Plantago major* leaf extract. *Phytotherapy Research*, 2000, 14:617–622.
69. Velasco-Lezama R et al. Effect of *Plantago major* on cell proliferation *in vitro*. *Journal of Ethnopharmacology*, 2006, 103:36–42.
70. Caceres A et al. Plants used in Guatemala for the treatment of gastrointestinal disorders. 1. Screening of 84 plants against enterobacteria. *Journal of Ethnopharmacology*, 1990, 30:55–73.
71. Pargas AR et al. In vitro antifungal activity of a *Plantago major* l. cream. *Revista Cubana de Plantas Medicinales*, 1996, 1:9–12.
72. Hetland G et al. Protective effect of *Plantago major* l. Pectin polysaccharide against systemic *Streptococcus pneumoniae* infection in mice. *Scandinavian Journal of Immunology*, 2000, 52:348–355.
73. Ponce-Macotela M et al. In vitro antigiardiasic activity of plant extracts. *Revista de Investigación Clinica*, 1994, 46:343–347.
74. Atta AH, El-Sooud AK. The antinociceptive effect of some Egyptian medicinal plant extracts. *Journal of Ethnopharmacology*, 2004, 95:235–238.

Herba Polygoni avicularis

Definition

Herba Polygoni avicularis consists of the whole or cut dried flowering aerial parts of *Polygonum aviculare* L. (Polygonaceae) (*1*, *2*).

Synonyms

Polygonum agreste Sumn., *P. aphyllum* Krock., *P. araraticum* Kom., *P. arenastrum* Boreau., *P. heterophyllum* Lindm., *P. viviparum* (*3–6*).

Selected vernacular names

Allseed nine-joints, armstrong, aviculaire, baekjeol, beggarweed, bian xu, birdgrass, bird knotgrass, bird's tongue, birdweed, bistorta centinodio, bistorte aviculare, Blutkraut, centinode, centinodia, common knotgrass, common knotweed, coreggiuola, cow grass, crawlgrass, chveulebrivi matitela, devil's grass, doejipool, doorweed, eunmadeup, gorets ptitsii, harilik linnurohi, herba centumnodii, herba sanguinalis, herbe à cochon, herbe aux panaris, herbe de renouée des oiseaux, herbe des St Innocents, hogweed, höusegräs, hundred jointed, knicker, knot-grass, knotgrass herb, knotweed, knot-weed, qush toron, laufrasen, madeupnamul, mat-grass, maura sūrene, ninety-knot, pig-rush, pigweed, pihatatar, pinkweed, plattsaad, poligono, poligono degli uccelli, porcfu, prostrate knotweed, rdesno ptaci, red robin, renouée des oiseaux, russischer knöterichtee, sanguinaire, saugrss, saukraut, schweinegrass, schweinekruse, sekedeknä, shabat el ghûl, sparrow tongue, sporiș, sporysz, stonegrass, swine's grass, swynel grass, tire-goret, traînasse, trampgrass, traniane, troscot, tungress, vej-pileurt, vogelknöterich, vogelknöterichkraut, way grass, wegetred, wegetritt, weggras, wegkruast, weidemannscher tee, Zerrgras (*4*, *6–18*).

Geographical distribution

Widespread in the temperate zones throughout the world. A common weed (*3*, *7*, *9*, *16*, *20*).

Description

An annual highly polymorphous plant, small taproot with numerous rootlets. Stems, branched, many prostrate or slightly ascendant, 10–60(100) cm in length, with longitudinal grooves, hairless. Leaves, alternate, petiolate or sessile, oblong to lanceolate or linear, hairless, apex pointed, up to 3 cm long, with pointed and toothed stipules. Ochrea covering the nodes, transparent, silvery, 4–12 mm long, bilobed, later cut into a few narrow strips, 8–10-veined. Flowers, hermaphrodite, entomophile, axillary, solitary or 2–5 fascicled, very small, inconspicuous, greenish-red; peduncle 1–1.5 mm long; calyx with 5 sepals, green with white or pink margins, 1.5–3.5 mm long; 5 petals, 2.5–3.5 mm long; 8 stamens; superior ovary with 3 very short styles and inconspicuous stigmata. Fruits, triangular nutlets, ovate to almost elliptical, as long as the epicalyx or protuberant, striated, flattish or concave faces, dark brown to black, minutely roughened, 2–4 mm long (*3*, *4*, *7*, *9*, *21–28*).

Plant material of interest: dried aerial parts

General appearance

Whole or cut leafy stems up to 40 cm in length. Stem is 0.5–2 mm thick, branched, with nodes, cylindrical or slightly angular and longitudinally striated; bears sessile or shortly petiolate, glabrous entire leaves. Leaves differ widely in shape and size: broad-elliptic, oblong, obovate, lanceolate or nearly linear, up to 3 cm long and 1 cm wide. The sheath-like stipules (ochrea) are lacerate and silvery. The flowers are small and axillary, they have 5 greenish-white perianth segments, the tips of which are often coloured red. The fruits are 2–4 mm long, brown to black triangular nutlets, usually punctate or striate (*1*, *2*).

Organoleptic properties

Odour: slight; taste: slightly astringent (*2*).

Microscopic characteristics

Cells of upper and lower epidermises have thick, straight, polygonal to sinuous cell walls. Cell walls of upper epidermis occasionally irregularly thickened. Cuticle is longitudinally striated at the leaf edge and on the largest veins. Stomata anisocytic. 1–3 layers of epidermis cells at the leaf margins have strongly thickened cell walls, which have been transformed into papilla-like protuberances. In the mesophyll of the leaves, and in the stems, there are numerous, sometimes very large, clusters of calcium oxalate crystals. There are many sinuous thick-walled fibres, especially on the upper and lower veins, and at the leaf edge.

Powdered plant material

Greenish-brown. Fragments of the leaf epidermis with polygonal to sinuous cell walls and numerous anisocytic stomata; fragments of leaves and stems containing numerous calcium oxalate clusters, some of them very large; groups of thick-walled fibres from the hypodermis of the stem; globular pollen grains with smooth exine and 3 germinal pores; occasional brown fragments of the exocarp composed of cells with thick sinuous walls.

General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography for the presence of characteristic constituents, caffeic acid and chlorogenic acid (*1*) or flavonoids (*29*), and colour reaction of cut drug with aluminium chloride for the detection of flavonoids (*2*) and colour reaction of water extract of pulverized drug with ferric chloride (*30*).

Using a 675 g/l solution of potassium hydroxide and gently heating, the epidermis of the leaves and a few cells of the mesophyll stain red to reddish-violet when examined using a 0.1 g/l solution of ferric chloride, some leaf fragments stain almost black (*1*, *2*, *7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*31*).

Chemical

No information available.

Foreign organic matter

Not more than 2% of roots and not more than 2% of other foreign matter (*1*, *2*). Brownish and blackish parts of plant, not more than 3%. For cut drug: not more than 10% of fragments of drug having a diameter less than 0.5 mm and not more than 10% of fragments of drug having a diameter more than 7 mm (*2*). Not more than 3% (*30*).

Total ash

Not more than 10% (*1*), 13% (*2*, *30*).

Acid-insoluble ash

Not more than 3% (*30*).

Sulfated ash
No information available.

Water-soluble extractive
Not less than 6% (*30*).

Alcohol-soluble extractive
Not less than 16% (*30*).

Loss on drying
Not more than 10% (*1*) or 13% (*2*). Not more than 15% (*30*).

Pesticide residues
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*1*). For other pesticides, see the *European pharmacopoeia* (*1*) and the WHO guidelines on quality control methods for medicinal plant materials (*31*) and pesticide residues (*32*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*31*).

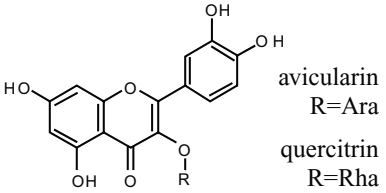
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*31*) for the analysis of radioactive isotopes.

Other purity tests
The content of mineral matter not more than 2% (*2*). Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.3% of total flavonoids, expressed as hyperoside (*1*) or not less than 0.5% of flavonoids, expressed as avicularin (*2*).

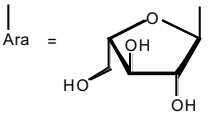
Major chemical constituents
The major constituents of the aerial parts are flavonoids (0.1–1%, rarely 2.5–3%): derivatives of kaempferol, quercetin and myricetin, especially avicularin (quercetin-3-*O*-arabinoside, approximately 0.2%); juglanin (kaempferol-3-*O*-arabinoside), hyperoside, quercitrin, rhamnetin-3-*O*-

galactoside, vitexin, isovitexin and rhamnazin hydrogen sulfate. There is also a lignan glycoside, aviculin, a naphthoquinone (6-methoxyplumbagin), a mucilage, which on hydrolysis produces galacturonic acid, glucose, galactose, arabinose and rhamnose; lignan aviculin; some tannins (rhatannin), phenolcarboxylic (e.g. caffeic and chlorogenic) acids, hydroxycoumarins (umbelliferone and scopoletin); tartaric, formic and silicic acid (approximately 1%), a small amount of which is present as water-soluble silicates (*4*, *7*, *8*, *19*, *20*, *33–43*). The structures of the main constituents are presented below.

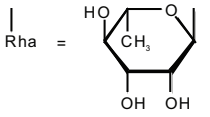


avicularin
R=Ara

quercitrin
R=Rha



α-L-arabinofuranosyl



α-L-rhamnopyranosyl

Medicinal uses

Uses supported by clinical data

Used for the supportive treatment of gingivitis (*44*).

Uses described in pharmacopoeias and well established documents

Herba Polygoni avicularis is used for the relief of cough and cold symptoms (*35*). The plant is well known in Chinese medicine where it is used for the treatment of urinary infection with difficult painful urination, as a remedy for heavy menstrual bleeding, for dysentery, snake bites, eczema and vulval itching (*29*).

Uses described in traditional medicine

Herba Polygoni avicularis has been used for lowering blood pressure, and as a haemostatic, anti-rheumatic, antipyretic and hypoglycaemic agent (*36*, *45–48*). It is also used for treatment of intestinal discomfort, to pass kidney stones, to treat varices, as a cholagogue and emmenagogue (*49–51*). The use of Herba Polygoni avicularis as an insecticide or vermifuge, astringent, antifungal and wound-healing agent has been described (*52–54*). It is also used for the treatment of weeping eczema (*55*).

Pharmacology

Experimental pharmacology

Antihepatotoxic activity

The antihepatotoxic activity of a methanol extract of dried Herba Polygoni avicularis was tested in rats. Intraperitoneal administration of the extract as a single dose of 1000 mg/kg body weight (bw) (about 0.2 g per rat) (represented as the amount of crude drug equivalent) inhibited alkaline phosphatase, serum aspartate aminotransferase activity and decreased plasma bilirubin concentrations when hepatotoxicity was induced by α-naphthylisothiocyanate. At a dose of 14.7 mg/kg the extract also inhibited serum alanine amino transaminase activity, induced by α-naphthylisothiocyanate. The extract (200 and 500 mg/kg bw) was hepatoprotective in conditions of carbon tetrachloride-induced hepatotoxicity. Methanol extracts of the crude drug demonstrated hepatoprotective effects by inhibiting lipid peroxide formation induced by adenosine diphosphate + nicotinamide adenine dinucleotide phosphate and carbon tetrachloride in rats at median inhibitory concentrations (MICs) of 21.6 µg/ml and 29.1 µg/ml, respectively (*56–58*). Intragastric administration of a methanol extract at a dose of 100 mg/kg bw, to male rats, reduced serum aspartate aminotransferase and alanine amino transaminase activities and the hydroxyproline content in the liver. In addition, the extract significantly reduced inflammation and fibrosis of the liver in a bile duct ligation model (*59*).

A free-radical scavenging effect was observed in vitro with a methanol extract of dried Herba Polygoni avicularis at an MIC of 89 µg/plate (*36*, *60*). Two flavonoids, avicularin and juglanin, were isolated from Herba Polygoni avicularis as the active constituents from the ethanol-acetic fraction by bioassay. Avicularin and, to a lesser extent, juglanin inhibited the lipid peroxidation of rat liver induced by 50% ethanol. Avicularin, the main constituent of the plant, significantly decreased the elevated serum aspartate aminotransferase and lactate dehydrogenase levels in carbon tetrachloride-intoxicated rats, demonstrating hepatoprotective properties. Avicularin also significantly decreased the serum bilirubin level in α-naphthylisothiocyanate-intoxicated rats. These results confirm the hepatoprotective activity of avicularin against chemically induced hepatotoxicity in rats (*61*).

The protective effects of a methanol extract of Herba Polygoni avicularis against liver fibrosis in rats were studied in a bile duct ligation and scission operation model, for 4 weeks. In rats that had been operated on, the levels of aspartate aminotransferase, alanine amino transaminase, al-

kaline phosphatase, total bilirubin in serum and hydroxyproline content in liver were dramatically increased. Treatment with the extract in rats that had been operated on reduced the serum aspartate aminotransferase, alanine amino transaminase and alkaline phosphatase levels significantly ($p < 0.01$). Liver hydroxyproline content was also reduced to 40% by treatment with the extract as compared with controls ($p < 0.01$). The morphological characteristics of fibrotic liver, which appeared in the control group of animals that had been operated on were less marked in the group that had been both operated on and treated with the extract. These results suggest that Herba Polygoni avicularis has an antifibrotic effect in rats (*59*).

Antiaggregatory effects

The antiaggregatory effects of vitexin, isovitexin, luteolin, kaempferol-3-arabinoside, rhamnetin-3-galactoside and quercetin-3-galactoside, active constituents isolated from Herba Polygoni avicularis, were tested in vitro, in platelet-rich plasma from blood donors. It was shown that vitexin and rhamnetin-3-galactoside, at a concentration of 10^{-5} M, inhibited the aggregation of human blood platelets induced by adenosine diphosphate (concentration 10^{-5} M) and arachidonic acid (concentration 10^{-4} M), whereas luteolin and kaempferol-3- arabinoside slowed or stimulated aggregation, depending upon the experimental conditions. These findings suggest that constituents tested may influence platelet aggregation by possible interaction with the cyclooxygenase and lipoxygenase pathway of the arachidonic acid cascade in human platelets (*62*, *63*).

Angiotensin-converting enzyme inhibiting activity

A chromatographic fraction from Herba Polygoni avicularis, containing rhatannin and other tannins, at a concentration of 20 µg/ml, and a methanol-aqueous extract (1:1) at a concentration of 200 µg/ml, inhibited the activity of angiotensin-converting enzyme isolated from pig kidney in vitro. Both rhatannin and the tannin samples had potent inhibitory effects on angiotensin-converting enzyme with an MIC of 1.1 mg/ml and showed high specificity for this enzyme (*64*, *65*).

Anti-inflammatory effects

An aqueous extract of oven-dried Herba Polygoni avicularis (at a concentration of 0.25 mg/ml) inhibited platelet activating factor in cell culture and platelet activating factor-induced neutrophil exocytosis. These findings may suggest a mechanism for the antiinflammatory action of the plant (*66*).

Antispasmodic activity

A 95% ethanol extract of Herba Polygoni avicularis had antispasmodic activity against barium-induced contractions at a concentration of 100 µg/ml in the isolated guinea-pig ileum (*67*). Hexane, ethyl acetate, and n-butanol extracts of Herba Polygoni avicularis were screened for potential vasorelaxant activity using isolated rat aorta. Hexane and n-butanol extracts exhibited distinctive vasorelaxant activity. The activity disappeared on removal of the functional endothelium or following pretreatment of the aortic tissues with *N*-nitro-L-arginine methyl ester, which is an inhibitor of nitric oxide synthase. These findings suggest that Herba Polygoni avicularis relaxes vascular smooth muscle via an endothelium-dependent nitric oxide mechanism (*68*).

Insect repellent activity

A 95% ethanol extract of dried Herba Polygoni avicularis, at a concentration of 1 g/l, was tested externally in hamsters as an insect repellent. The extract, at a dose of 2.5 µg/cm^2, had insect repellent activity against the sand fly, *Lutzomyia longipalpis*, a major vector of leishmaniasis in South America (*69*).

Toxicology

The LD_{50} of a 50% ethanol extract of the aerial parts of Polygoni avicularis administered by the intraperitoneal route in rats was determined to be 500 mg/kg bw (*70*). Tests with a 10% infusion, decoction (1:4), aqueous extract (1:50) and an ethanol extract of the leaves were conducted in mice, cats, rabbits and dogs. The minimal lethal dose for cats and rabbits was determined to be 20 ml/kg for the infusion or decoction, and 2 ml/kg for the aqueous extract, when administered intravenously. For mice, the minimal lethal dose was determined to be 0.2 ml (about 10 ml/kg) for the aqueous extract, when administered intraperitoneally. Intravenous injections lowered blood pressure in cats, rabbits and dogs. The most potent preparations were the aqueous and ethanol extracts (*71*).

Clinical pharmacology

The effectiveness of a natural extract of *Polygonum aviculare* was assessed in 60 students (18–25 years old). Over a period of 2 weeks they used the extract (1 mg/ml) in an oral rinse twice daily. The O'Leary Plaque Index and the Loe and Silness Gingivitis Index were recorded at baseline in all the subjects. The result showed that the extract decreased gingivitis from day 0 ($\bar{x}$x" height = "11" width = "13" ≥ 1.056) to day 14 ($\bar{x}$x" height = "11" width = "13" ≥ 1.011) ($p \leq 0.05$). The researchers concluded that the

extract in the form of an oral rinse can be included in supportive therapy for gingivitis (*44*).

Adverse reactions
No information was found.

Contraindications
No information was found.

Warnings
No information was found.

Precautions

General
No information was found.

Drug interactions
No information was found.
Should not be used together with an anticoagulant (see Pharmacology).

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
Use during pregnancy is not recommended (see Pharmacology).

Nursing mothers
No information was found.

Paediatric use
No information was found.

Dosage forms
Ground herb for infusions and other Galenical preparations for internal use and for local application (*8*).

Posology

(Unless otherwise indicated)
Daily dose: 4–6 g of drug; or equivalent preparations (*35*).
For internal use. Infusion: to 3 tablespoons (15 g) of the herb, add 200 ml of boiling water and allow to stand for 15 minutes; divide 75 ml of the infusion into three parts and drink three times daily, 20–40 minutes before meals (*72*). A cup of the tea is prepared by placing 1.5 g of the chopped drug into cold water, heating to boiling, and straining after 10 minutes, 3–5 times a day (*7*).

References

1. *European Pharmacopoeia,* 5th ed. Suppl. 5.2. Strasbourg, European Pharmacopoeia Commission, 2005.
2. *USSR pharmacopoeia*, 11th ed. *Vol 2*. Moscow, Meditsina, 1990.
3. Chevallier A. *The encyclopedia of medicinal plants*. London, Dorling Kindersley, 1996.
4. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific, 2001.
5. *Armenian national formulary for herbal medicines*. Yerevan, Drug and Medical Technology Agency Ministry of Health of RA JSC, 2001.
6. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
7. Bisset NG, Wichtl M. *Herbal drugs and phytopharmaceuticals: a handbook for practice on a scientific basis.* Stuttgart, Medpharm Scientific Publishers, 1994.
8. Fleming T, ed. *Physicians' desk reference (PDR) for herbal medicines*. Montvale, Medical Economics Company, 2000.
9. *Weed species* (http://weedman.horsham.net.au/weeds/).
10. *Northern Ontario plant database* (http://www.northernontarioflora.ca).
11. Muravjova DA. *Farmakognozija*. Moscow, Meditsina, 1978.
12. Īriste V, Eniņa V. *Ārstniecības augu vārdnīca.* Riga, Medikamentu informācijas centers, 2000.
13. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
14. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.
15. Istudor V. *Farmacognozie, fitochimie, fitoterapie.* Bucharest, Editura Medicala, 1998.
16. Bedevian AK. *Illustrated polyglottic dictionary of plant names*. Cairo, Medbouly Library, 1994.
17. Parsa A. *Flore de L'Iran*. *Vol. VIII*. Tehran, University of Tehran, 1960.
18. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
19. Yakovlev GP, Blinova KF, ed. *Rastenija dlja nas.* St Petersburg, Utchebnaja kniga, 1996.

20. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
21. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
22. Grieve M. *A modern herbal.* London, Tiger Books, 1998.
23. Komarov VL, ed. *Flora SSSR. Vol. 5.* Pod red. Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1936.
24. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR.* Izd. Moscow, Mysli, 1976.
25. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR.* 3-ie izd. Kishinev, Shtiintsa, 1986.
26. *Botaniceskii atlas.* Mosva, Izdatel'stvo selskohozeaistvennoi literatury, jurnalov i plakatov, 1963.
27. Muravjova DA. *Farmakognozija.* Moscow, Meditsina, 1991.
28. Grinkevici NI, Ladiginoi EI. *Pharmacognozia. Atlas. Pod red.* Moscow, Meditsina, 1989.
29. *Pharmacopoeia of the People's Republic of China*. *Vol. 1*. Beijing, State Pharmacopoeia Commission of the Ministry of Public Health, 2005.
30. *The Korean herbal pharmacopoeia*. Seoul, Korea Food and Drug Administration, 2002.
31. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
32. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
33. Yakovlev GP, Blinova KF, ed. *Lekarstvennoje rastitel'noje syr'yo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
34. Wren RC. *Potter's new cyclopedia of botanical drugs and preparations.* Essex, CW Daniel, 1988.
35. Blumenthal M et al, eds. *The Complete German Commission E monographs. Therapeutic guide to herbal medicines.* Austin, TX, American Botanical Council, 1998.
36. Kim HJ, Woo ER, Park H. A novel lignan and flavonoids from *Polygonum aviculare*. *Journal of Natural Products*, 1994, 57:581–586.
37. *Rastitel'nye resursy SSSR*. *Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Magnoliaceae-Limoniaceae. Vol. 1*. Leningrad, Nauka, 1984.
38. *Rastitel'nye resursy.* St Petersburg, RAN, 1996.
39. Al-Hazimi HMA, Haque SN. A new naphthoquinone from Polygonum aviculare. *Natural Product Letters*, 2002, 16:115–118.
40. Swiatek L, Dombrowicz E. Phenolic acids in medicinal plant drugs of *Polygonum* species. *Farmacja Polska*, 1987, 43:420–423.
41. Zhao A et al. Chemical studies on *Polygonum aviculare. Tianran Chanwu Yanjiu Yu Kaifa*, 2002, 14:29–32.

42. Vysochina GI. Dynamics of content and component composition of flavonoids in *Polygonum aviculare* L. *Rastitel'nye Resursy*, 1999, 35:67–74.
43. Smolarz HD. Flavonoid glycosides in nine *Polygonum* L. taxons. *Acta Societatis Botanicorum Poloniae,* 2002, 71:29–33.
44. Gonzalez Begne M et al. Clinical effect of a Mexican sanguinaria extract (*Polygonum aviculare* L.) on gingivitis. *Journal of Ethnopharmacology*, 2001, 74:45–51.
45. Novaretti R, Lemordant D. Plants in the traditional medicine of the Ubaye Valley. *Journal of Ethnopharmacology*, 1990, 30:1–34.
46. Beal JL. One man's quest for plant constituents of therapeutic value. *Economic Botany*, 1990, 44:4–11.
47. Rivera D, Obon C. The ethnopharmacology of Madeira and Porto Santo islands, a review. *Journal of Ethnopharmacology*, 1995, 46:73–93.
48. Darias V et al. Hypoglycaemic plants from the Canary Islands. *Phytotherapy Research Supplement*, 1996, 10:S3–S5.
49. Boukef K, Souissi HR, Balansard G. Contribution to the study on plants used in traditional medicine in Tunisia. *Plant Medicine and Phytotherapy*, 1982, 16:260–279.
50. Grodzinskii AM, ed. *Lekarski roslini. Entsiklopedichnyi dovidnik.* Kiiv, Redaktsija Ukrain'skoi entsiklopedii, 1991.
51. De Feo V et al. Traditional phytotherapy in the Peninsula Sorrentina, Campania, Southern Italy. *Journal of Ethnopharmacology*, 1992, 36:113–125.
52. Rios Jl, Recio MC, Villar A. Antimicrobial activity of selected plants employed in the Spanish Mediterranean area. *Journal of Ethnopharmacology*, 1987, 21:139–152.
53. Schmeda-Hirschmann G, Rojas De Arias A. A screening method for natural products on triatomine bugs. *Phytotherapy Research*, 1992, 6:68–73.
54. Zargari A. *Medicinal plants. Vol. 4*, 5th ed. Tehran, University of Tehran, 1992 (Tehran University Publications, No. 1810/4).
55. Duke JA, Ayensu ES. *Medicinal plants of China. Reference publications.* Book 2, *Vol. 4*. Algonac, MI, Reference Publications 1985:363–705.
56. Kumazawa N et al. Protective effects of various methanol extracts of crude drugs on experimental hepatic injury induced by carbon tetrachloride in rats. *Yakugaku Zasshi*, 1990, 110:950–957.
57. Kumazawa N et al. Protective effects of various methanol extracts of crude drugs on experimental hepatic injury induced by alpha-naphthylisothiocyanate in rats. *Yakugaku Zasshi*, 1991, 111:199–204.
58. Ishizuka O et al. Effects of various methanol extracts of crude drugs on experimental subacute and chronic hepatic injury. *Yakugaku Zasshi*, 1992, 112:174–182.
59. Nan JX et al. Antifibrotic effects of the methanol extract of *Polygonum aviculare* in fibrotic rats induced by bile duct ligation and scission. *Biological and Pharmaceutical Bulletin*, 2000, 23:240–243.

60. Cha BC et al. Antioxidative effect of domestic plants. *Korean Journal of Pharmacognosy*, 1997, 28:15–20.
61. Choi Hyuck Jai et al. Anti-lipid peroxidation and liver protective effects of *Polygonum aviculare* L. *Saengyak Hakhoechi*, 1997, 28:117–123.
62. Amroyan EA, Panosyan AG, Gabrielyan ES. Izutchenie vlijanija flavonoidov i rodstvennykh im soedinenii na agregaciju trombocitov [Study of the influence of flavonoids and related compounds of herbal origin on the platelet aggregation]. *Tesisy dokladov konferencii po problemam fiziko-khimicheskoi biologii i biotekhnologii v medicine*. Yerevan, Armenia, Scientific Council of the Ministry of Health, 1984.
63. Panosyan AG et al. The effect of *Polygonum aviculare* L. flavonoids on platelet aggregation. *Khiniko-Farmatsevticheskii Zhurnal*, 1986, 20:190–194.
64. Inokuchi JI et al. Inhibitors of angiotensin converting enzyme in crude drugs. I. *Chemical and Pharmaceutical Bulletin*, 1984, 32:3615–3619.
65. Inokuchi JI et al. Inhibitors of angiotensin-converting enzyme in crude drugs. II. *Chemical and Pharmaceutical Bulletin*, 1985, 33:264–269.
66. Tunon H, Olavsdotter C, Bohlin L. Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis. *Journal of Ethnopharmacology*, 1995, 48:61–76.
67. Itokawa H et al. Studies on the constituents of crude drugs having inhibitory activity against contraction of the ileum caused by histamine or barium chloride. *Shoyakugaku Zasshi*, 1983, 37:223–228.
68. Yin Ming Hao et al. Screening of vasorelaxant activity of some medicinal plants used in Oriental medicines. *Journal of Ethnopharmacology*, 2005, 99:113–117.
69. Arias RJ, Schmeda-Hirschmann G, Falcao A. Feeding deterrency and insecticidal effects of plant extracts on *Lutzomyia longipalpis*. *Phytotherapy Research*, 1992, 6:64–67.
70. Hager-ROM. Polygonun avicularis herba. In: *Hagers Handbuch der Drogen und Arzneistoffe*. Springer Verlag, Heidelberg, 2003.
71. Aluf MA, Raspopova TV. Pharmacology of *Polygonum aviculare*. *Farmakologiya i Toksikologiya* (Moscow), 1945, 8:34–35.
72. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennym rastenijam* [*Textbook of medicinal plants*]. Moscow, Meditsina, 1988.

Folium Salviae

Definition

Folium Salviae consists of the whole or cut dried leaves of *Salvia officinalis* L. (Lamiaceae) (*1*, *2*) collected during the summer from cultivated plants (*2*).

Synonyms

Salvia chromatica et papillosa Hoffmg., *S. cretica* L., *S. grandiflora* Ten., *S. maior et minor* Gmeli, *S. tomentosa* Mill (*3*, *4*).

Selected vernacular names

Aci elma out, ada çayi, aedsalvei, ārstniecības salvija, asfâqs, broad-leafed sage, broad-leaved white sage, cinstes, cinstet, cocean-capresc, common sage, dalmatian sage, dalmatiner-Salbei, dorivor marmarak, dorivor mavrak, echte salvei, echter Salbei, Edelsalbei, edler Salbei, elalisphakos, elelisphakos, fischsalbe, garden sage, Garten Salbei, gradinski tshai, grande sauge, green sage, guiāh-e-tchai, herbe cacrée, jaleş, kharnah, konski bosilek, Königssalbei, Königs-Salbei, maryam-goli, maryamíyah, narrow-leaved white sage, petite sauge, sabikraut, Salbei, salbey, sale, salie, salfei, salva, salvetta, salvia fina, salvia grande, salvia officinale, salvia real, salvia salvatrix, salvie, samkurnalo salbi, saudzette, sauge, sauge commune, sauge officinale, save, sawge, Scharlachkraut, scharlei, shalfei lekarstvennyi, shop sage, szalvia, serialu, serlaiu, Rauch-Salbei, red sage, té della grecia, thé de gréce, the de france, tibbi adacayi, true sage, tugensalbe (*3*, *5–16*).

Geographical distribution

Indigenous to the whole Mediterranean region. Cultivated worldwide (*3*, 5, *6*, *17–20*).

Description

A perennial subshrub, 25–50(–70) cm high, woody root. Stems wiry, woody at the base, erect, branched, quadrangular, hollow and softly curly-pubescent. Leaves, opposite, simple, petiolate, from oblong-ovate

to lanceolate (sometimes with two small lobes at the base), round or wedge-shaped base, round or subacute apex, crenulate margins, finely wrinkled by a strongly-marked network of veins on both sides, upper and lower surfaces greyish-green, softly hairy and glandular, 2–10 cm long, 0.8–1.5(–4)cm wide. Inflorescences, loose spikes of flower whorls. Flowers, bisexual, zygomorphic, 2 cm long, bluish-violet or purplish, sometimes white. Bracts, sessile, ovate-lanceolate, acuminate, membranous, and striated at the base. Peduncles, curly-pubescent, 3–6 mm long. Calyx, campanulate, membranous, striated, downy (especially outside on the veins and the margins of the sepals), bilabiate; the upper lip 3-toothed; the lower bifid; all the teeth subulate and acuminate, 9–10 mm long. Corolla, 2 or 3 times as long as the calyx, with a large projecting tube, ringed on the inside, and bilabiate; upper lip arched, lower lip trilobed, the lateral lobes being reflexed. Pistil, single, superior 4-lobed ovary. The two usually absent upper stamens are sometimes present in very small-sterile hooks. Fruit, 4 nutlets, nearly round, brown, 2.5 mm in diameter (*5*, *8*, *17*, *18*, *21–26*).

Plant material of interest: dried leaves

Fresh material may also be used, provided that when dried it complies with the monograph in the *European Pharmacopoeia* (*27*).

General appearance

The lamina of whole leaf is about 2–10 cm long and up to 3 cm wide, oval, oblong-ovate, elliptical to lanceolate; upper surface pubescent, lower surface tomentose, texture soft and velvety. The margin is finely crenulate to smooth. The apex is rounded or subacute and the base is shrunken at the petiole and rounded or cordate. Both surfaces with conspicuous, reticulate venation. The deeply depressed venation on the upper surface is very prominent on the lower surface and shows a dense network of raised veinlets. The upper surface is pale green and finely granular; the lower surface is greyish-green to white and pubescent. Petiole up to about 4 cm. The cut drug consists of small leaf fragments, which, because of the dense tomentum, cling together; the fine pubescence on both surfaces and the reticulate venation on the lower surface are easily recognized (*1*, *5*, *28*, *29*).

Organoleptic properties

Odour: intensely spicy and aromatic; taste: spicy, aromatic, bitter and slightly astringent (*2*, *5*).

Microscopic characteristics

Dorsiventral with a two-layered palisade; epidermal cells are polygonal and thick-walled; upper epidermis with markedly beaded anticlinal walls and a faintly striated cuticle; lower epidermal cells sinuous; diacytic stomata on both epidermises, more frequent on the lower one; abundant covering and glandular trichomes on both epidermises and also on the petiole; covering trichomes long, narrow, uniseriate, with thick walls, 2–6 celled, with a short basal cell, undulating terminal cells tapering to sharply acute apexes; the glandular trichomes of two types: typical labiate type with a unicellular stalk and a radiate eight-celled head containing reddish-brown secretion, or smaller with a one to four-celled uniseriate stalk and a unicellular or bicellular head (*1*, *2*, *5*, *25*, *29–31*).

Powdered plant material

Grey to brownish-green. Numerous articulated and bent trichomes with narrow elongated cells and very thick cell walls at the base as well as fragments of these trichomes; fragments of the upper epidermis with pitted, somewhat polygonal cells; fragments of the lower epidermis with sinuous cells and numerous diacytic stomata; rare single glandular trichomes with a unicellular or bicellular head and a stalk consisting of 1–4 cells; abundant glandular trichomes with a unicellular stalk and a head composed of 8 radiating cells with a raised common cuticle; groups of vascular tissues from the petiole and main veins showing vessels with annular and reticulate thickening (*1*, *29*).

General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography in daylight and under ultraviolet light for the presence of characteristic essential oil constituents, α-thujone, β-thujone and cineole (*1*, *29*) and other characteristic terpenes (*5*). Thin-layer chromatographic study of the flavonoids (*32*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*33*).

Chemical

No information available.

Foreign organic matter

Not more than 2% (*1*) or not more than 3% (*2*, *32*). Not more than 5% of brownish and blackish leaves. Not more than 13% of other parts of plant (flowers and fragments of stems). For cut drug, not more than 10% of fragments of drug having a diameter less than 0.5 mm (*2*). Leaves of *Salvia triloba* absent (*34*).

Total ash

Not more than 10% (*1*). Not more than 8% (*29*). Not more than 12% (*2*).

Acid-insoluble ash

Not more than 2% (*29*).

Sulfated ash

Not more than 12% (*34*).

Water-soluble extractive

Not less than 16% (*29*).

Alcohol-soluble extractive

No information available.

Loss on drying

Not more than 14% (*2*). Not more than 10% (*1*).

Pesticide residues

The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*1*). For other pesticides, see the *European pharmacopoeia* (*1*) and the WHO guidelines on quality control methods for medicinal plant materials (*33*) and pesticide residues (*35*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*33*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*33*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, acid-insoluble ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national require-

ments. The content of mineral matter not more than 0.5% (*2*); not more than 3% of foreign matter (*29*).

Chemical assays

Contains not less than 1.5% (v/w) of essential oil for the whole drug and not less than 1.0% (v/w) of essential oil for the cut drug (*1*). Not less than 0.8% of essential oil (*2*). High-performance liquid chromatography method for determination of the thujone content (*36*). Hexane extract is coloured red by sodium hydroxide (thujone) (*37*).

Major chemical constituents

Dried leaves contain 1–3.5% essential oil (fresh leaves contain about 3 times less), mostly monoterpenoids of which 18–60% are α-thujone, 3–21% β-thujone, 4.5–24.5% camphor (both (R)-(+)-camphor and (S)-(–)-camphor may be found), 5.5–13% cineole, 0–12% humulene, 1–6.5% α-pinene, 1.5–7% camphene, 0.5–3% limonene, up to 1% linalool, and up to 2.5% bornyl acetate. Sesquiterpenoids such as veridiflorol (11%) and humulene (0–12%), a diterpenoid, manool (9%), and a linear aliphatic alcohol 1-octen-3-ol (8.5%) are present among the main constituents of the essential oil. Sage leaves of Dalmatian origin consist mainly of α-thujone and β-thujone (share 20–60%), 1,8-cineole (6–16%) and camphor (14–37%) (*3*, *5*, *7*, *23*, *27*, *36*, *38*, *39*, *40*). Also, apianane terpenoids, 3–8% condensed catechin-type tannins (salviatannin); phenolic acids (rosmarinic, chlorogenic, ferulic and gallic acids; caffeic acid monomers, dimers, trimers and tetramers); 1–3% flavonoids (apigenin and luteolin 7-*O*-glucosides, genkwanin, genkwanin-6-methyl ether, 5-methoxysalvigenin, hispidulin); diterpenes (carnosol, carnosic acid, rosmanol, safficinolide); triterpenes (oleanolic acid, ursolic acid, α-amyrin, β-amyrin (about 5%)); and resin are present (*3*, *5*, *7*, *23*, *38*, *39*, *41–51*). The structures of the characteristic constituents are presented below.

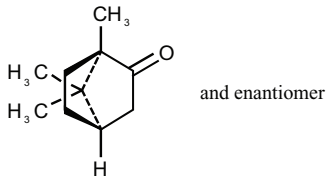
Medicinal uses

Uses supported by clinical data

The management of mild to moderate Alzheimer disease (*52*).

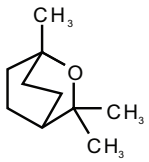
Uses described in pharmacopoeias and well established documents

Salvia officinalis is used internally for treatment of influenza, bronchitis, sinusitis, meningitis and neuritis (*53*). The European Scientific Cooperative on Phytotherapy supports the use of *S. officinalis* leaves for stomatitis and gingivitis (*27*). The German Standard Licence for *S. officinalis* infu-

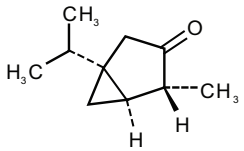


and enantiomer

camphor

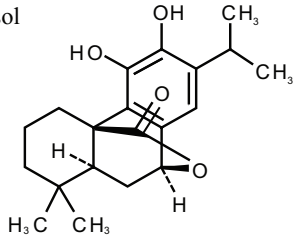


cineole

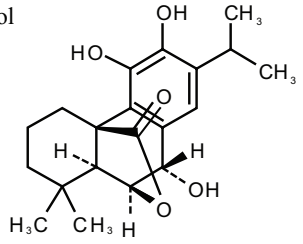


thujone

carnosol



rosmanol



sion also indicates its use for the supportive treatment of dyspeptic symptoms and gastrointestinal catarrh (*5*).

Uses described in traditional medicine

Traditionally *S. officinalis* has been used to treat hoarseness and coughs (*54*, *55*). It is also used as a sedative, tonic, and stimulant (*56*). *Salvia officinalis* has a long history of use as a restorative of lost or declining cognitive functions in Western European systems of traditional medicine (*57*). *Salvia officinalis* leaves are also used for treatment of haemorrhages, hyperhydrosis, galactorrhoea and dysentery (*58–60*). In traditional Italian medicine, they are used to treat rheumatism (*61*, *62*). The use of *S. officinalis* for the treatment of menstrual disorders has been reported (*63*, *64*). It is also used to treat acne, hair loss and dandruff, as a vulnerary and an antiseptic (*65*, *66*).

Pharmacology

Experimental pharmacology

Antioxidant activity

A 95% ethanol and an aqueous-ethanol (1:1) extract of dried leaves of *S. officinalis* demonstrated antioxidant activity in vitro at concentrations of 0.01% and 0.025%, respectively, against 2,2´-azobis(2-amidinopropane) dihydrochloride-induced liposome peroxidation (*67*, *68*). A fat-soluble ex-

tract of *S. officinalis* leaves exhibited antioxidant effects against lipid peroxidation in cooked beef homogenate at a concentration of 30 µg/ml (*69*). Aqueous and aqueous-ethanol (1:1) extracts of the dried leaves increased scavenging of diphenylpicrylhydrazyl radical and superoxide anions at a concentration of 0.025%, as determined by the neotetrazolium method in vitro (*70*). Acetone, ethanol-acetic acid, and hexane extracts of the dried leaves exhibited antioxidant activity at a concentration of 0.01% when tested on rapeseed and sunflower oils (*71*). The median effective dose for antioxidant activity of an aqueous-ethanol extract of the dried leaves and a tannin fraction isolated from the dried flowering top and leaves were determined to be 41 mg/ml and 23.1 µg/ml, respectively by a colorimetric assay in vitro (*45*). The protective effect of *Salvia* against enzyme-dependent and enzyme-independent lipid peroxidation was evaluated. A 50% aqueous-methanol extract of dried leaves was found to be more effective than the positive control, alpha-tocopherol acid succinate. A 50% aqueous-ethanol extract inhibited lipid peroxide formation in brain homogenate in vitro at a median inhibitory concentration of 2.7 µg/ml in enzyme-dependent and 8.98 µg/ml in enzyme-independent systems of lipid peroxidation (*72*).

In vitro cultures of hepatocytes isolated from rats drinking a *Salvia officinalis* infusion (2 g of dried leaves in 150 ml of water) and challenged with the oxidant *tert*-butyl hydroperoxide (0.75 or 1.0 mM), showed a significantly higher glutathione content and glutathione reductase activity (10%) after 4 hours of culture when compared with rats drinking water without the extract, and subjected to the same treatment. The compounds present in the *S. officinalis* infusion thus improve the liver antioxidant potential (*73*). An aqueous-ethanol (1:1) extract of the leaves at a concentration of 0.5 µg/ml, expressed cytoprotective activity in a cell culture of mouse fibroblasts under conditions of active oxygen-induced cell damage (*68*).

Hepatoprotective action

The protective effects of an aqueous extract of *S. officinalis* leaves against the hepatotoxic effects of the anti-metabolite azathioprine, which resulted in acute oxidative damage to the liver, were tested. Administration of azathioprine induced oxidative stress through depletion of antioxidants and elevating the level of malondialdehyde in the liver combined with escalation of alanine aminotransferase and aspartate aminotransferase in the serum. Pretreatment with the extract produced a protective effect against azathioprine-induced hepatotoxicity: animals under investigation failed to show necrosis of the liver after azathioprine administration, and also most parts of the livers were histologically normal. In addition, the extract blocked the elevation of the levels of aminotransferase and aspar-

tate aminotransferase in the serum, and reduced the malondialdehyde level in the liver (*74*).

Antimicrobial activity

The antimicrobial activity of a chloroform extract of the dried leaves was tested in vitro. The extract was active against *Staphylococcus aureus*, *Mycobacterium phlei* and *Candida albicans*, at minimum inhibitory concentrations (MICs) of 4.6, 2.3 and > 9.2 g/l/agar plate (grams of dry leaves per litre of culture medium), respectively. The methanol extract of dried leaves also demonstrated antimicrobial activity against *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycobacterium phlei* and *Candida albicans* with MIC values > 18.9 g/l/agar plate (*75*). An aqueous extract of the leaves exhibited activity against *Escherichia coli* (MIC = 1.3 mg/100 ml/agar plate), *Enterococcus faecalis* (MIC = 10 mg/ml), and *Bacillus subtilis* (MIC = 7.7 mg/ml) (*76*). The antifungal activity of the ethanol-aqueous extract (1:1) of dried leaves of *S. officinalis* was tested in vitro. At a concentration of 500 mg/ml (dose expressed as dry weight of the plant), the extract was weakly active against *Penicillium digitatum* (*77*).

Antiprotozoal, anthelminthic and insecticidal activity

At a concentration of 10 µg/ml, a methanol extract of the leaves demonstrated nematocidal activity in a cell culture against *Toxocara canis* (*78*). Acetone, carbon tetrachloride and methanol extracts of dried leaves, at a concentration of 100 mg/l, demonstrated insecticidal activity against *Spodoptera littoralis* (*79*).

Anti-inflammatory activity

In a model of ear inflammation, induced by 12-*O*-tetradecanoylphorbol-13-acetate, the ethyl acetate and hexane extracts of *S. officinalis* leaves demonstrated anti-inflammatory activity when applied externally to mice at a concentration of 20 µl/animal (*80*). In addition, antioedema activity was observed when a methanol extract of *S. officinalis* leaves was applied externally to mouse ears at a concentration of 2 mg/ear. The methanol extract had an inhibition ratio of 24 in a 12-*O*-tetradecanoylphorbol-13-acetate-induced ear inflammation model (*81*). The *n*-hexane and the chloroform extracts of the leaves dose-dependently inhibited croton oil-induced ear oedema in mice. The chloroform extracts were the most active. By contrast, the methanol extracts had a very small effect and the essential oil was inactive. The main active principle was identified as ursolic acid, which had a median inhibitory dose of 0.14 µM/cm^2 and was twice as potent as indomethacin (median inhibitory dose, 0.26 µM/cm^2) (*82*).

This study was an extension of earlier studies by Yasukawa et al. (*81*) and Okuyama et al. (*80*).

Cholinergic activity

Studies were carried out to evaluate the cholinergic receptor-binding activity of ethanol extracts prepared from leaves of *S. officinalis*. Plant extracts were screened for their ability to displace [^{3}H]-(*N*)-nicotine from nicotinic receptors and [^{3}H]-(*N*)-scopolamine from muscarinic receptors, in homogenates of human cerebral cortical cell membranes. The most potent extracts, prepared from three *Salvia* species had a median inhibitory concentration (IC_{50}) of < 1 mg/ml. The displacement curves of some of these extracts were comparable with that of carbamylcholine chloride, a potent acetylcholine analogue. Choline, a weak nicotinic ligand (IC_{50}, 3×10^{-4} M) was found in extracts at concentrations of $10^{-6} – 10^{-5}$ M. However, at the concentrations studied, choline accounted for only 5% of the displacement activity observed. Although most extracts screened expressed some nicotinic and muscarinic activity, only a few showed dose-dependent receptor activity typical of compounds with genuine cholinergic activity (*57*). Mnemogenic effects of the ethanol extract from the leaves of *S. officinalis* (50 mg/kg, administered intraperitoneally) were tested in rats. Interactions of the extract with the cholinergic system in memory retention of passive avoidance learning were investigated. Administration of the extract increased memory retention. Stimulation of muscarinic and nicotinic cholinoreceptors by pilocarpine (0.5 and 1 mg/rat) and nicotine (0.1 and 1 µg/rat) potentiated the response of the extract and increased memory retention ($F_{4,25} = 7.67$, $p < 0.001$) (*83*).

Neuroprotective effect

The effect of a standardized extract of the leaves of *S. officinalis* and its active ingredient rosmarinic acid on Alzheimer amyloid-β peptide (Aβ)-induced toxic effects in cultured rat pheochromocytoma PC12 cells was evaluated. Incubation of PC12 cells with Aβ (fragment 1-42) for 24 hours caused cell death and this effect was reduced by the extract, and by rosmarinic acid. Rosmarinic acid reduced a number of events induced by Aβ. These included formation of reactive oxygen species, lipid peroxidation, DNA fragmentation, caspase-3 activation, and tau protein hyperphosphorylation. Moreover, rosmarinic acid inhibited p-p38 mitogen-activated protein kinase, but not glycogen synthase kinase-3 activation. These data demonstrated a neuroprotective effect of *Salvia* leaf extract against Aβ-induced toxicity, which could support the use of this plant in the treatment of Alzheimer disease. Rosmarinic acid could contribute, at least in part, to the extract-induced neuroprotective effect (*84*).

Cardiovascular effects

Following intragastric administration of an ethanol-aqueous extract (1:1) of fresh leaves to rats, hypotensive activity, negative chronotropic effect and diuretic activity were observed. The concentration of the extract was roughly equivalent to 5 g fresh leaf material/kg body weight (bw) of the animal (results were significant at $p < 0.05$) (*85*, *86*).

Antihyperglycaemic activity

The antihyperglycaemic (antidiabetic) activity of an aqueous-ethanol extract of the dried leaves was studied in healthy male mice and in male mice with alloxan-induced diabetes. The extract significantly reduced the blood glucose concentration of fasting normal mice 120 minutes (15.7%) and 240 minutes (30.2%) after intraperitoneal administration ($p < 0.05$). The extract also significantly diminished the hyperglycaemia in mildly diabetic mice after 240 minutes (22.7%). The administration of the extract to animals with severe hyperglycaemia did not cause a significant decrease in blood glucose concentration (*87*). A dried methanol extract of the leaves of *S. officinalis* (100, 250, 400 and 500 mg/kg) was injected intraperitoneally to rats with streptozocin-induced diabetes. Blood samples were obtained before and after administration of the extract. The results showed that the extract decreased serum glucose in diabetic rats in 3 hours with no effect on insulin release from the pancreas. This effect was not seen in normal rats (*83*).

Antimutagenic activity

The antimutagenic activity of a terpenoid fraction of the dried leaves was tested in *Escherichia coli* strain K12 in vitro. At a concentration of 20 µg/ml, the terpenoid fraction demonstrated antimutagenic activity against ultraviolet-induced reversion of argE 3 ochre mutations (*88*). Acetone, ethyl acetate, methylene dichloride and hexane extracts of the dried leaves also expressed antimutagenic effects in vitro (concentration 10 µg/ml) in *Salmonella typhimurium* strain TA98 against 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole-induced mutagenesis (*89*). The antimutagenic properties of terpenoid fractions of *S. officinalis* leaves were tested in a mammalian system in vivo by examining the ability of the plant extracts to decrease the frequency of aberrant cells induced by a potent mutagen. Groups of mice were treated with three concentrations of terpenoid fractions. There was no significant difference between the frequency of aberrant cells after treatment with a concentration of 25 µl/kg and after treatment with the negative control (olive oil). However, at a concentration of 50 µl/kg, the frequency of aberrant cells was significantly de-

creased ($X^2_{(1)}$, 4.05; $p < 0.05$). At a concentration of 100 µl/kg the terpenoid fraction was cytotoxic. Mitomycin C, as a potent mutagen, was used for induction of chromosome aberrations. Treatment with terpenoid fractions (25 µl/kg and 50 µl/kg) significantly decreased the frequency of aberrations caused by mitomycin C ($X^2_{(1)}$, 5.42; $p < 0.02$: $X^2_{(1)}$, 14.93; $p < 0.001$, respectively). There was a dose–response relationship in which increasing concentrations of the plant extract caused decreases in the percentage of aberrations. Nontoxic concentrations of *S. officinalis* may be recommended for use as inhibitors of mutagenesis or carcinogenesis (*90*).

Toxicology

The neurotoxicity of thujone has been demonstrated in rats (*91*). The oral (median lethal dose LD_{50}) in the rat has been reported to be 500 mg/kg body weight (bw) (*92*). Thujone is much more acutely toxic after parenteral administration and the intravenous LD_{50} in rabbits is stated to be 0.031 mg/kg bw (*92*). The symptoms associated with acute intoxication are epileptiform convulsions with general vasodilatation, hypotension, retardation of the heartbeat and an increase in respiratory amplitude. In rats, intraperitoneal injections of thujone induced electrocortical seizures associated with myoclonic activity and the convulsant and lethal effects occurred at similar doses of 200 mg/kg bw (*93*). Several studies on the mechanism of the neurotoxicity of α-thujone indicate that it is a modulator of the gamma-aminobutyric acid-type A receptor (*94*). The principal manifestation of intoxication by thujone is epileptiform convulsions in animals and humans. The no-observable effects limit (NOEL) for convulsions in subchronic toxicity studies in female rats was 5 mg/kg bw administered orally (*93*). The LD_{50} of a methanol extract of the leaves of *S. officinalis* was determined to be 4000 mg/kg (*83*).

The safety and antioxidant potential of an infusion *of S. officinalis* leaves was assessed in vivo by measuring plasma transaminase, liver glutathione reductase and glutathione-*S*-transferase activities in mice and rats. Replacing water with the infusion for 14 days did not affect the body weight or food consumption of the rodents. Liver toxicity was not induced by the infusion. However, significant increases of liver glutathione-*S*-transferase activity were observed in 24% of rats and 10% of mice receiving the infusion (*68*).

Clinical pharmacology

The objective of a multicentre, randomized, placebo-controlled, parallel group study was to assess the efficacy and safety of an *S. officinalis* ex-

tract (1:1 in 45% alcohol) using a fixed dose (60 drops/day), in patients with Alzheimer disease, over a 4-month period. Patients with mild to moderate Alzheimer disease aged between 65 and 80 years (n = 42, 18 women) with a score of ≥ 12 on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and ≤ 2 on the Clinical Dementia Rating (CDR) were randomly allocated to either receive a placebo or a fixed dose of *S. officinalis* extract. ADAS-cog is a subscale of 11 items that evaluates selected aspects of attention, language, memory, orientation, praxis and reasoning. CDR (sum of the boxes) provides a consensus-based global clinical measure by summing the ratings from six domains: memory, orientation, judgement, problem-solving, community affairs, home and hobbies, and personal care. Over a 16-week period, the primary outcome measure was the change in the ADAS-cog score. Change in CDR (sum of the boxes) was the secondary outcome of the trial. In addition, side-effects were systematically recorded throughout the study using a checklist. The results showed that at 4 months, the extract led to a better outcome for cognitive functions than placebo (ADAS-cog: F, 4.77; df, 1; p, 0.03) (CDR-SB: F, 10.84; df, 1; $p < 0.003$). There were no significant differences between the two groups in terms of observed side-effects except for agitation, which appeared to be more frequent in the group treated with the placebo ($p = 0.09$). The results of the study indicate that the extract was efficacious in the management of mild to moderate Alzheimer disease (*52*).

Adverse reactions

After prolonged ingestion of ethanol extracts of leaves of *Salvia officinalis*, epileptiform convulsions can occur (*38*).

Contraindications

In view of the toxicity of the plant due to the thujone and camphor content, extracts should be used with caution and not ingested in large amounts (*95*). Because of the known toxic properties of thujone, the described abortifacient properties (*96*), and lack of safety data concerning administration of Folium Salviae and its preparations in children as well as during pregnancy and lactation, it is contraindicated in these patient groups (*38*, *97*).

Warnings

Long-term use of essential oil (more than 2 weeks at a time) should be avoided (*98*).

Precautions

General

Extracts of the herb should be used with caution and should not be ingested in large amounts or over prolonged periods. Caution is required with the use of ethanol preparations of the leaves because of the presence of thujone and camphor (*27*). If symptoms worsen or persist for longer than 1 week or in any case of unclear symptoms, such as night sweats, increased body temperature or loss of weight, a physician should be consulted (*98*).

Drug interactions

Salvia officinalis may interfere with existing hypoglycaemic and anticonvulsant therapies, and may increase the sedative effects of simultaneously used drugs, and central effects of alcohol (*95*). *S. officinalis* may interfere with absorption of iron and other minerals (*98*).

Drug and laboratory test interactions

No information was found.

Carcinogenesis, mutagenesis, impairment of fertility

No information was found.

Pregnancy

Use in pregnancy is not recommended (See Contraindications).

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Dosage forms

Cut herb for infusions, ethanol extracts and distillates for gargles, rinses and other topical applications, as well as for internal use. In addition, the fresh plants may be pressed to yield a juice (*38*).

Posology

(Unless otherwise indicated)

Internal. Daily dose: 4 g of drug or equivalent preparations (*38*). Infusion: one tablespoon of an infusion (4 g of the leaf) in 200 ml of boiling water, three times daily (*38*, *95*). Tincture: 75 drops of a tincture (1:10 in 55% or

70% ethanol), three times daily (*27*, *32*). Fluidextract: 1–4 ml (1:1 in 45% ethanol), three times daily (*95*). Dry extract: 160 mg of dry aqueous extract corresponding to 880 mg of drug, three times daily (*27*).
For gargles and rinses. Infusion: 3 g of herb or 2–3 drops of essential oil in 150 ml of water (*27*). Tincture: 1:10 in 70% ethanol. Extract: 5 g of ethanol extract in 1 glass water (*20*).
External. Cataplasm or irrigation: 30 g of cut herb in 200 ml of boiling water for 20 min, applied to affected area (*19*).

References

1. *European pharmacopoeia*. 5th ed. Strasbourg, Council of Europe, 2005.
2. *USSR pharmacopoeia*. 11th ed. Vol. 2. Moscow, Meditsina, 1990.
3. Brendler T, Grünwald J, Jänicke C, eds. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific, 2001.
4. Blaschek W et al., eds. *HagerROM 2003. Hagers Handbuch der Drogen und Arzneistoffe*. Heidelberg, Springer Verlag, 2003.
5. Bisset NG, Wichtl M. *Herbal drugs and phytopharmaceuticals: a handbook for practice on a scientific basis.* Stuttgart, Medpharm Scientific Publishers, 1994.
6. Petkov V, ed. *Sovremennaja fitoterapija.* Sofia, Meditsina i fizkultura, 1988.
7. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
8. Kirtikar KR, Basu BD. *Indian medicinal plants.* In 4 vols. Delhi, M/S Bishen Singh Mahendra Pal Singh, 1918.
9. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
10. Īriste V, Eniņa V. *Ārstniecības augu vārdnīca.* Riga, Medikamentu informācijas centers, 2000.
11. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
12. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.
13. Grigorescu E, Ciulei I, Ursula S. *Index fitoterapeutic.* Bucharest, Editura Medicala, 1986.
14. Bedevian AK. *Illustrated polyglottic dictionary of plant names*. Cairo, Medbouly Library, 1994.
15. Parsa A. *Flore de L'Iran*. Volume VIII. Tehran, University of Tehran, 1951.
16. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
17. Muravjova DA. *Farmakognozija.* Moscow, Meditsina, 1991.
18. Hammerman AF, Kadaev GN, Jacenko-Khmelevski AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
19. Lager AA. *Fitoterapija*. Krasnojarsk, Izdatel'stvo krasnojarskogo universiteta, 1988.

20. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.
21. Grieve M. *A modern herbal the medicinal, culinary, cosmetic and economic properties, cultivation and folk-lore of herbs, grasses, fungi, shrubs & trees with their modern scientific uses.* London: Tiger Books International, 1992 (http://www.botanical.com/botanical/mgmh/s/sages-05.html).
22. Bunney S, ed. *The illustrated encyclopaedia of herbs and their medicinal and culinary uses.* Prague, Chancellor Press, 1993.
23. Yakovlev GP, Blinova KF, eds. *Lekarstvennoje rastitel'noje syr'yo. Farmakognozija.* St Petersburg, SpetzxLit, 2004.
24. Komarov VL, Shishkin BK. *Flora SSSR. Vol. 21. Pod red.* Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1954.
25. Grinkevici NI, Ladigina EI eds. *Pharmacognozia. Atlas*. Pod red. Moscow, Meditsina, 1989.
26. Prodan I, Buia AL. *Flora mica ilustrata a Republicii populare Romine*. Bucharest, Editura Agro-silvica de stat, 1958.
27. *ESCOP monographs*. *Salviae folium. The Scientific Foundation for Herbal Medicinal Products,* 2nd ed. Exeter, European Scientific Cooperative on Phytotherapy, 2003.
28. Kuznetsova MA, Rybatshuk IZ. *Farmakognozija.* Moscow, Meditsina, 1984.
29. *British herbal pharmacopoeia,* Vol. 2. Exeter, British Herbal Medicine Association, 1996.
30. *British herbal pharmacopoeia,* Vol. 1. Bournemouth, British Herbal Medicine Association, 1983.
31. Toma C, Rugină R. *Anatomia plantelor medicinale – Atlas*. Bucharest, Ed. Academiei României, 1998.
32. *Deutsches Arzneibuch* [*German pharmacopoeia*], 10th ed. 1st Supplement 1992; 2nd Supplement 1993.
33. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
34. *Pharmacopoeia Helvetica,* 4 vols. 7th ed. Berne, Département federal de l'intérieur, 1987.
35. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
36. Radulescu V, Chiliment S, Oprea E. Capillary gas chromatography-mass spectrometry of volatile and semi-volatile compounds of *Salvia officinalis. Journal of Chromatography* A, 2004, 1027:121–126.
37. *Bruneton J. Pharmacognosie. Phytochimie. Plantes medicinales,* 2nd ed. Paris, Lavoisier, 1993.
38. Blumenthal M et al., eds. *The Complete German Commission E monographs. Therapeutic guide to herbal medicines.* Austin, TX, American Botanical Council, 1998.

39. Yakovlev GP, Blinova KF, ed. *Rastenija dlja nas.* St Petersburg, Utchebnaja kniga, 1996.
40. Miladinović D, Miladinović L. Antimicrobial activity of essential oil of sage from Serbia. *Facta Universitatis*, 2000, 2:97–100.
41. Miura K, Kikuzaki H, Nakatani N. Apianane terpenoids from *Salvia officinalis*. *Phytochemistry*, 2001, 58:1171–1175.
42. Lu Y, Foo LY. Polyphenolics of *Salvia* – a review. *Phytochemistry*, 2002, 59:117–140.
43. Fleming T, ed. *Physicians desk reference (PDR) for herbal medicines.* Montvale, Medical Economics, 2000.
44. Wang M et al. Isolation and structural elucidation of two new glycosides from sage (*Salvia officinalis*). *Journal of Agricultural and Food Chemistry*, 2000, 48:235–238.
45. Lamaison JL, Petitjean-Freytet C, Carnat A. Rosmarinic acid, total hydroxycinnamic derivative contents and antioxidant activity of medicinal Apiaceae, Boraginaceae and Lamiaceae. *Annales Pharmaceutiques Françaises*, 1990, 48:103–108.
46. Lamaison JL et al. Rosmarinic acid and content and antioxidant activity in French Lamiaceae. *Fitoterapia*, 1991, 62:166–171.
47. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Magnoliaceae-Limoniaceae*. Vol. 6. Leningrad, Nauka, 1991.
48. Raal A, Orav A, Arak E. Composition of the essential oil of *Salvia officinalis* L. from various European countries. *Natural Product Research*, 2007, 21:406–411.
49. Ravid U, Putievsky E, Katzir I. Determination of the enantiomeric composition of (1R)(+)- and (1S)(–)-camphor in essential oils of some Lamiaceae and Compositae herbs. *Flavour and Fragrance Journal*, 1993, 8:225–228.
50. Hossein Mirjalili M et al. Essential oil variation of *Salvia officinalis* aerial parts during its phenological cycle. *Chemistry of Natural Compounds*, 2006, 42:19–23.
51. Then M et al. Polyphenol-, mineral element content and total antioxidant power of sage (*Salvia officinalis* L.) extracts. *Acta Horticulturae,* 2004, 629 (*Future for Medicinal and Aromatic Plants*): 123–129 (http://www.actahort.org/books/629/629_16.htm).
52. Akhondzadeh S et al. *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. *Journal of Clinical Pharmacy & Therapeutics*, 2003, 28:53–59.
53. Franchomme P et al. *L'aromathérapie exactement. Encyclopédie de l'utilisation thérapeutique des huiles essentielles*. Limoges, Roger Jollois Editeur, 1990.
54. De Feo V et al. Traditional phytotherapy in the Peninsula Sorrentina, Campania, Southern Italy. *Journal of Ethnopharmacology*, 1992, 36:113–125.

55. Stehmann JR, Brandao MGL. Medicinal plants of Lavras Novas (Minas Gerais, Brazil). *Fitoterapia*, 1995, 56:515–520.
56. Elisabetsky E, Figueiredo W, Oliveria G. Traditional Amazonian nerve tonics as antidepressant agents: Chaunochiton Kappleri: a case study. *Journal of Herbs Spices and Medicinal Plants*, 1992, 1:125–162.
57. Wake G et al. CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. *Journal of Ethnopharmacology*, 2000, 69:105–114.
58. Vazquez FM, Sauarez MA, Perez A. Medicinal plants used in the Barros area, Badajoz province (Spain). *Journal of Ethnopharmacology*, 1997, 44:81–85.
59. Bisset NG, ed. *Herbal drugs and phytopharmaceuticals*, 2nd ed. Stuttgart, Medpharm Scientific Publishers, 2001.
60. Snajder K. *Use of indigenous medicinal plants against dysentery and diarrhea in vicinity of Trstenik (Central Serbia).* Belgrade, Serbian Radova Sapadnika Institute Ispitivaye Lekovit Biya, 1951:21.
61. Lokar LC, Poldini L. Herbal remedies in the traditional medicine of the Venezia Giulia region (North East Italy). *Journal of Ethnopharmacology*, 1988, 22:231–239.
62. De Feo V, Senatore F. Medicinal plants and phytotherapy in the Amalfitan coast, Salerno province, Campania, Southern Italy. *Journal of Ethnopharmacology*, 1993, 39:39–51.
63. Holeman M et al. Comparative chemical study of the essential oils of *Salvia officinalis*, *Salvia aucheri*, *Salvia verbenaca*, *Salvia phlomoides* and *Salvia argentea*. *Fitoterapia*, 1984, 55:143–148.
64. Rivera D, Obon C. The ethnopharmacology of Madeira and Porto Santo islands, a review. *Journal of Ethnopharmacology*, 1995, 46:73–93.
65. Bellakhdar J et al. Repertory of standard herbal drugs in the Moroccan pharmacopoeia. *Journal of Ethnopharmacology*, 1991, 35:123–143.
66. Gray AM, Flatt PR. Nature's own pharmacy: the diabetes perspective. *Proceedings of Nutrition Society*, 1997, 56:507–517.
67. Djarmati Z et al. High antioxidant activity of extracts obtained from sage by supercritical CO2 extraction. *Journal of the American Oil Chemistry Society*, 1991, 68:731–734.
68. Masaki H et al. Active-oxygen scavenging activity of plant extracts. *Biological and Pharmaceutical Bulletin*, 1995, 18:162–166.
69. Wong JW, Hashimoto K, Shibamoto T. Antioxidant activities of rosemary and sage extracts and vitamin E in a model meat system. *Journal of Agriculture and Food Chemistry*, 1995, 43:2707–2712.
70. Kirby AJ, Schmidt RJ. The antioxidant activity of Chinese herbs for eczema and of placebo herbs. I. *Journal of Ethnopharmacology*, 1997, 56:103–108.
71. Nguyen HTT, Pokorny J, Korcazk J. Antioxidant activities of rosemary and sage extracts in rapeseed and sunflower oils. *Czech Journal of Food Sciences*, 1999, 17:121–126.

72. Zupko I et al. Antioxidant activity of leaves of Salvia species in enzyme-dependent and enzyme-independent systems of lipid peroxidation and their phenolic constituents. *Planta Medica*, 2001, 67:366–368.
73. Cristovao F et al. The drinking of a Salvia officinalis infusion improves liver antioxidant status in mice and rats. *Journal of Ethnopharmacology*, 2005, 97:383–389.
74. Amin A, Hamza AA. Hepatoprotective effects of Hibiscus, Rosmarinus and Salvia on azathioprine-induced toxicity in rats. *Life Sciences*, 2005, 77:266–278.
75. Recio MC, Rios JL, Villar A. Antimicrobial activity of selected plants employed in the Spanish Mediterranean area. Part II. *Phytotherapy Research*, 1989, 3:77–80.
76. Brantner A, Grein E. Antibacterial activity of plant extracts used externally in traditional medicine. *Journal of Ethnopharmacology*, 1994, 44:35–40.
77. Guerin JC, Reveillere HP. Antifungal activity of plant extracts used in therapy. II. Study of 40 plant extracts against 9 fungi species. *Annales Pharmaceutiques Françaises*, 1985, 43:77–81.
78. Kiuchi F. Studies on the nematocidal constituents of natural medicines. *Natural Medicine*, 1995, 49:364–372.
79. Jannet HB et al. Responses of *Spodoptera littoralis* larvae to Tunisian plant extracts and to neo-cleodane diterpenoids isolated from *Ajuga pseudoiva* leaves. *Fitoterapia*, 2000, 71, 2:105–112.
80. Okuyama T et al. Studies on cancer bio-chemoprevention of natural resources. X. Inhibitory effect of spices on TPA-enhanced 3H-choline incorporation in phospholipid of C3HL0TL/2 cells and on TPA-induced ear edema. *Zhonghua Yaoxue Zazhi*, 1995, 47:421–430.
81. Yasukawa K et al. Inhibitory effect of edible plant extracts on 12-o-tetradecanoylphorbol-13-acetate-induced ear oedema in mice. *Phytotherapy Research*, 1994, 7:185–189.
82. Baricevic D et al. Topical anti-inflammatory activity of *Salvia officinalis* L. leaves: the relevance of ursolic acid. *Journal of Ethnopharmacology*, 2001, 75:125–132.
83. Eidi M, Eidi A, Zamanizadeh H. Effect of *Salvia officinalis* L. leaves on serum glucose and insulin in healthy and streptozocin-induced diabetic rats. *Journal of Ethnopharmacology*, 2005, 100:310–313.
84. Juvone T et al. The spice sage and its active ingredient rosmarinic acid protect PC12 cells from amyloid-β peptide-induced neurotoxicity. *Journal of Pharmacology and Experimental Therapeutics Fast Forward*, 2006 as DOI:10.1124/jpet.105.099317.
85. De A Ribeiro R et al. Acute antihypertensive effect in conscious rats produced by some medicinal plants used in the state of Sao Paulo. *Journal of Ethnopharmacology*, 1986, 15:261–269.

86. De A Ribeiro R et al. Acute diuretic effects in conscious rats produced by some medicinal plants used in the state of Sao Paulo, Brazil. *Journal of Ethnopharmacology*, 1988, 24:19–29.
87. Alarcon Aguilar FJ et al. Investigation on the hypoglycaemic effects of extracts of four Mexican medicinal plants in normal and alloxan-diabetic mice. *Phytotherapy Research*, 2002, 16:383–386.
88. Simic D et al. Antimutagenic effect of terpenoids from sage (*Salvia officinalis* l.). *Journal of Environmental Pathology, Toxicology and Oncology*, 1997, 16:293–301.
89. Samejima K et al. Luteolin: a strong antimutagen against dietary carcinogen, TRP-P-2, in peppermint, sage, and thyme. *Journal of Agriculture and Food Chemistry*, 1995, 43:410–414.
90. Vujošević M, Blagojević J. Antimutagenic effects of extracts from Sage (*Salvia officinalis*) in mammalian system *in vivo*. *Acta Veterinaria Hungarica*, 2004, 52:439–443.
91. Millet Y et al. Toxicity of some essential plant oils. Clinical and experimental study. *Clinical Toxicology*, 1981, 18:1485–1498.
92. *Opinion of the Scientific Committee on Food on Thujone*. Brussels, European Commission Health & Consumer Protection Directorate-General, 2003 (SCF/CS/FLAV/FLAVOUR/23 ADD2 Final, 6 February).
93. *Opinion of the Scientific Committee on Food on thujone*. Brussels, European Commission, Scientific Committee on Food, 2002.
94. Höld KM et al. *α-thujone (the active component of absinthe); γ-aminobutyric acid type A receptor modulation and metabolic detoxification*. TOXI 023, 219th ACS National Meeting, San Francisco, CA, March 2000.
95. Newall CA et al., eds. *Herbal medicines. A guide for health-care professionals*. London, Pharmaceutical Press, 1996.
96. Farnsworth NR. Potential value of plants as sources of new antifertility agents 1. *Journal of Pharmaceutical Sciences*, 1975, 64:535–598.
97. Ladynina EA, Morozova RS. *Fitoterapija*. Leningrad, Meditsina, 1987.
98. Longe JL, ed. *The Gale encyclopedia of alternative medicine*, 2nd ed. *Vol. 4*. Detroit, MI, Thomson, 2005.

Folium Sennae*

Definition

Folium Sennae consists of the dried leaflets of *Cassia senna* L. (Fabaceae).[1]

Synonyms

Fabaceae are also referred to as Leguminosae.

Although recognized as two distinct species in many pharmacopoeias (*1–8*), *Cassia acutifolia* Delile and *C. angustifolia* Vahl. are considered botanically to be synonyms of the single species *Cassia senna* L. (*9*).

Selected vernacular names

Alexandria senna, Alexandrian senna, cassia, eshrid, falajin, fan xie ye, filaskon maka, hindisana, illesko, Indian senna, ma khaam khaek, makhaam khaek, mecca senna, msahala, nelaponna, nelatangedu, nilavaka, nilavirai, nubia senna, rinji, sanai, sand hijazi, sanjerehi, sen de alejandria, sen de la india, senna makki, senna, senamikki, sennae folium, sonamukhi, Tinnevelly senna, true senna (*3*, *10–14*).

Description

Low shrubs, up to 1.5 m high, with compound paripinnate leaves, having 3–7 pairs of leaflets, narrow or rounded, pale green to yellowish green. Flowers, tetracyclic, pentamerous, and zygomorphic, have quincuncial calyx, a corolla of yellow petals with brown veins, imbricate ascendent prefloration, and a partially staminodial androeceum. The fruit is a broadly elliptical, somewhat reniform, flattened, parchment-like, dehiscent pod, 4–7 cm long by 2 cm wide, with 6 to 10 seeds (*11*, *14*, *15*).

Plant material of interest: leaflets

General appearance

Macroscopically, the leaflets are lanceolate or lanceolate-ovate, unequal at the base, with entire margin, acute-mucronate apex and short, stout peti-

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.

[1] C. italica Mill. is listed in the Malian pharmacopoeia.

oles; sometimes broken; 1.5–5 cm in length and 0.5–1.5 cm in width, bearing a fine pubescence of appressed hairs, more numerous on the lower surface (*1–7*).

Organoleptic properties

The colour is weak yellow to pale olive (*1*, *2*). The odour is characteristic, and the taste is mucilage-like and then slightly bitter (*1*, *3*).

Microscopic characteristics

Epidermis with polygonal cells containing mucilage; unicellular thick-walled trichomes, length, up to 260 µm, slightly curved at the base, warty; paracytic stomata on both surfaces; under the epidermal cells a single row of palisade layer; cluster crystals of calcium oxalate distributed throughout the lacunose tissue; on the adaxial surface, sclerenchymatous fibres and a gutter-shaped group of similar fibres on the abaxial side containing prismatic crystals of calcium oxalate (*1*).

Powdered plant material

Light green to greenish yellow. Polygonal epidermal cells showing paracytic stomata. Unicellular trichomes, conical in shape, with warty walls, isolated or attached to fragments of epidermis. Fragments of fibrovascular bundles with a crystal sheath containing calcium oxalate prisms. Cluster crystals isolated or in fragments of parenchyma (*2*, *3*).

Geographical distribution

The plant is indigenous to tropical Africa. It grows wild near the Nile river from Aswan to Kordofan, and in the Arabian peninsula, India and Somalia (*15*). It is cultivated in India, Pakistan, and the Sudan (*11*, *12*, *14*, *15*).

General identity tests

Macroscopic, microscopic examinations, and microchemical analysis (*1–6*), and thin-layer chromatographic analysis for the presence of characteristic sennosides (sennosides A–D) (*3–5*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Folium Sennae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*16–18*). For preparation of decoction: aerobic bacteria—10^7/g; moulds and yeast—10^5/g; *Escherichia coli*—10^2/g; other enterobacteria—

10^4/g. Preparations for internal use: aerobic bacteria—10^5/g; moulds and yeast—10^4/g; *Escherichia coli*—0/g; other enterobacteria—10^3/g.

Foreign organic matter

Not more than 2.0% of stems (*1*) and not more than 1.0% of other foreign organic matter (*1*, *4*, *8*).

Total ash

Not more than 12% (*5*).

Acid-insoluble ash

Not more than 2.0% (*1*, *8*).

Water-soluble extractive

Not less than 3% (*1*).

Moisture

Not more than 10% (*6*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Folium Sennae is not more than 0.05 mg/kg (*18*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*16*) and guidelines for predicting dietary intake of pesticide residues (*19*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*16*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*16*).

Other purity tests

Chemical tests and tests of alcohol-soluble extractive are to be established in accordance with national requirements.

Chemical assays

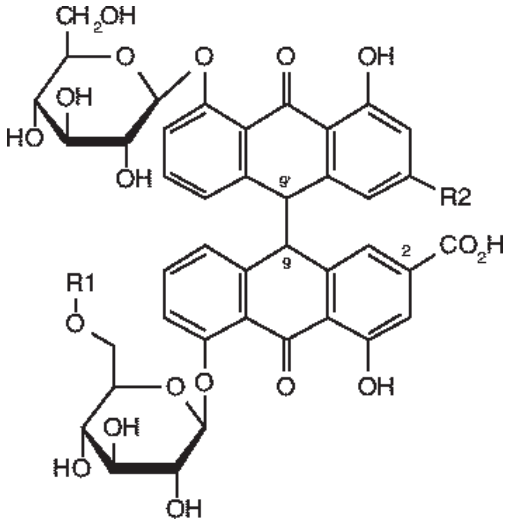
Contains not less than 2.5% of hydroxyanthracene glycosides, calculated as sennoside B (*1*, *4*, *5*). Quantitative analysis is performed by

spectrophotometry (*1*, *4–8*) and by high-performance liquid chromatography (*20*).

Thin-layer chromatography is employed for qualitative analysis for the presence of sennosides A and B (*3–5*).

Major chemical constituents

Folium Sennae contains a family of hydroxyanthracene glycosides, the most plentiful of which are sennosides A and B. There are also small amounts of aloe-emodin and rhein 8-glucosides, mucilage, flavonoids, and naphthalene precursors (*15*).



	R1	R2	9-9'
sennoside A	H	CO_2H	*R*,R* (threo)*
sennoside B	H	CO_2H	*R*,S* (erythro)*
sennoside C	H	CH_2OH	*R*,R* (threo)*
sennoside D	H	CH_2OH	*R*,S* (erythro)*
sennoside E	CO-CO_2H	CO_2H	*R*,R* (threo)*
sennoside F	CO-CO_2H	CO_2H	*R*,S* (erythro)*

Dosage forms

Crude plant material, powder, oral infusion, and extracts (liquid or solid) standardized for content of sennosides A and B (*15*, *21*, *22*). Package in well-closed containers protected from light and moisture (*1–8*).

Medicinal uses

Uses supported by clinical data

Short-term use in occasional constipation (*21–25*).

Uses described in pharmacopoeias and in traditional systems of medicine

None.

Uses described in folk medicine, not supported by experimental or clinical data

As an expectorant, a wound dressing, an antidysenteric, and a carminative agent; and for the treatment of gonorrhoea, skin diseases, dyspepsia, fever, and haemorrhoids (*11*, *23*, *25*).

Pharmacology

Experimental pharmacology

The effects of Folium Sennae are due primarily to the hydroxyanthracene glucosides, especially sennosides A and B. These β-linked glucosides are secretagogues that increase net secretion of fluids and specifically influence colonic motility and enhance colonic transit. They are not absorbed in the upper intestinal tract; they are converted by the bacteria of the large intestine into the active derivatives (rhein-anthrone). The mechanism of action is twofold: (1) effect on the motility of the large intestine (stimulation of peristaltic contractions and inhibition of local contractions), resulting in an accelerated colonic transit, thereby reducing fluid absorption, and (2) an influence on fluid and electrolyte absorption and secretion by the colon (stimulation of mucus and active chloride secretion), increasing fluid secretion (*24*, *25*).

Clinical pharmacology

The time of action of senna is usually 8–10 hours, and thus the dose should be taken at night (*24*). The action of the sennosides augments, without disrupting, the response to the physiological stimuli of food and physical activity (*24*). The sennosides abolish the severe constipation of patients suffering from severe irritable bowel syndrome (*26*). In therapeutic doses, the sennosides do not disrupt the usual pattern of defecation times and markedly soften the stool (*24*). Sennosides significantly increase the rate of colonic transit (*27*) and increase colonic peristalsis, which in turn increase both faecal weight and dry bacterial mass (*24*, *28*). Due to their colonic specificity, the sennosides are poorly absorbed in the upper gastrointestinal tract (*29*).

Toxicity

The major symptoms of overdose are griping and severe diarrhoea with consequent losses of fluid and electrolytes. Treatment should be supportive with generous amounts of fluid. Electrolytes, particularly potassium, should be monitored, especially in children and the elderly.

Contraindications

As with other stimulant laxatives, the drug is contraindicated in persons with ileus, intestinal obstruction, and stenosis, atony, undiagnosed abdominal symptoms, inflammatory colonopathies, appendicitis, abdominal pains of unknown cause, severe dehydration states with water and electrolyte depletion, or chronic constipation (*21*, *30*). Folium Sennae should not be used in children under the age of 10 years.

Warnings

Stimulant laxative products should not be used when abdominal pain, nausea, or vomiting are present. Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition (*31*). Chronic abuse, with diarrhoea and consequent fluid electrolyte losses, may cause dependence and need for increased dosages, disturbance of the water and electrolyte balance (e.g. hypokalaemia), atonic colon with impaired function, albuminuria and haematuria (*29*, *32*).

The use of stimulant laxatives for more than 2 weeks requires medical supervision.

Chronic use may lead to pseudomelanosis coli (harmless).

Hypokalaemia may result in cardiac and neuromuscular dysfunction, especially if cardiac glycosides (digoxin), diuretics, corticosteroids, or liquorice root are taken (*29*).

Precautions

General

Use for more than 2 weeks requires medical attention (*21*, *31*).

Drug interactions

Decreased intestinal transit time may reduce absorption of orally administered drugs (*32*, *33*).

The increased loss of potassium may potentiate the effects of cardiotonic glycosides (digitalis, strophanthus). Existing hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs, such as quinidine, which affect potassium channels to change sinus rhythm. Simultaneous use with other drugs or herbs which

induce hypokalaemia, such as thiazide diuretics, adrenocorticosteroids, or liquorice root, may exacerbate electrolyte imbalance (*21*, *22*).

Drug and laboratory test interactions

Urine discoloration by anthranoid metabolites may lead to false positive test results for urinary urobilinogen, and for estrogens measured by the Kober procedure (*32*).

Carcinogenesis, mutagenesis, impairment of fertility

No in vivo genotoxic effects have been reported to date (*34–37*). Although chronic abuse of anthranoid-containing laxatives was hypothesized to play a role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated (*38–40*).

Pregnancy: non-teratogenic effects

Use during pregnancy should be limited to conditions in which changes in diet or fibre laxatives are not effective (*41*).

Nursing mothers

Use during breastfeeding is not recommended owing to insufficient data on the excretion of metabolites in breast milk (*21*). Small amounts of active metabolites (rhein) are excreted into breast milk, but a laxative effect in breastfed babies has not been reported (*21*).

Paediatric use

Contraindicated for children under 10 years of age (*21*).

Other precautions

No information available on teratogenic effects in pregnancy.

Adverse reactions

Senna may cause mild abdominal discomfort such as colic or cramps (*21*, *22*, *33*). A single case of hepatitis has been described after chronic abuse (*42*). Melanosis coli, a condition which is characterized by pigment-loaded macrophages within the submucosa, may occur after long-term use. This condition is clinically harmless and disappears with cessation of treatment (*33*, *43*, *44*).

Long-term laxative abuse may lead to electrolyte disturbances (hypokalaemia, hypocalcaemia), metabolic acidosis or alkalosis, malabsorption, weight loss, albuminuria, and haematuria (*21*, *22*, *33*). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant

laxatives are repeatedly used (*21*, *33*). Conflicting data exist on other toxic effects such as intestinal-neuronal damage due to long-term misuse (*45–54*).

Posology

The correct individual dose is the smallest required to produce a comfortable, soft-formed motion (*21*). Powder: 1–2 g of leaf daily at bedtime (*11*). Adults and children over 10 years: standardized daily dose equivalent to 10–30 mg sennosides (calculated as sennoside B) taken at night.

References

1. *The international pharmacopoeia*, 3rd ed. *Vol. 3. Quality specifications*. Geneva, World Health Organization, 1988.
2. *The United States Pharmacopeia XXIII.* Rockville, MD, US Pharmacopeial Convention, 1996.
3. *African pharmacopoeia*, 1st ed. Lagos, Organization of African Unity, Scientific, Technical & Research Commission, 1985.
4. *British pharmacopoeia.* London, Her Majesty's Stationery Office, 1988.
5. *European pharmacopoeia*, 2nd ed. Strasbourg, Council of Europe, 1995.
6. *Pharmacopoeia of the People's Republic of China* (English ed.). Guangzhou, Guangdong Science and Technology Press, 1992.
7. *Deutsches Arzneibuch 1996*. Stuttgart, Deutscher Apotheker Verlag, 1996.
8. *Pharmacopée française*. Paris, Adrapharm, 1996.
9. Brenan JPM. New and noteworthy Cassia from tropical Africa. *Kew bulletin*, 1958, 13:231–252.
10. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, March 15, 1995 production (an on-line database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
11. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, Blakiston, 1950.
12. *Medicinal plants of India*, *Vol. 1.* New Delhi, Indian Council of Medical Research, 1976.
13. Huang KC. *The pharmacology of Chinese herbs*. Boca Raton, FL, CRC Press, 1994.
14. Farnsworth NR, Bunyapraphatsara N, eds. *Thai medicinal plants*. Bangkok, Prachachon, 1992.
15. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
16. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
17. *Deutsches Arzneibuch 1996. Vol. 2. Methoden der Biologie*. Stuttgart, Deutscher Apotheker Verlag, 1996.
18. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1997.

19. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva. World Health Organization, 1997 (unpublished document WHO/FSF/FOS/97.7).
20. Duez P et al. Comparison between high-performance thin-layer chromatography-fluorometry and high-performance liquid chromatography for the determination of sennosides A and B in Senna (*Cassia* spp.) pods and leaves. *Journal of chromatography*, 1984, 303:391–395.
21. Core-SPC for Sennae Folium. *Coordinated review of monographs on herbal remedies*. Brussels, European Commission, 1994.
22. German Commission E Monograph, Senna folium. *Bundesanzeiger*, 1993, 133:21 July.
23. Leng-Peschlow E. Dual effect of orally administered sennosides on large intestine transit and fluid absorption in the rat. *Journal of pharmacy and pharmacology*, 1986, 38:606–610.
24. Godding EW. Laxatives and the special role of Senna. *Pharmacology*, 1988, 36(Suppl. 1):230–236.
25. Bradley PR, ed. *British herbal compendium*, *Vol. 1*. Bournemouth, British Herbal Medicine Association, 1992.
26. Waller SL, Misiewicz JJ. Prognosis in the irritable-bowel syndrome. *Lancet*, 1969, ii:753–756.
27. Ewe K, Ueberschaer B, Press AG. Influence of senna, fibre, and fibre + senna on colonic transit in loperamide-induced constipation. *Pharmacology*, 47(Suppl. 1):242–248.
28. Stephen AM, Wiggins HS, Cummings JH. Effect of changing transit time on colonic microbial metabolism in man. *Gut*, 1987, 28:610.
29. *Goodman and Gilman's the pharmacological basis of therapeutics*, 9th ed. New York, McGraw-Hill, 1996.
30. *Physicians' desk reference*, 49th ed. Montvale, NJ, Medical Economics Company, 1995.
31. *American hospital formulary service.* Bethesda, MD, American Society of Hospital Pharmacists, 1990.
32. *United States pharmacopeia, drug information*. Rockville, MD, US Pharmacopeial Convention, 1992.
33. *Martindale, the extra pharmacopoeia*, 30th ed. London, Pharmaceutical Press, 1993.
34. Heidemann A, Miltenburger HG, Mengs U. The genotoxicity of Senna. *Pharmacology*, 1993, 47(Suppl. 1):178–186.
35. Tikkanen L et al. Mutagenicity of anthraquinones in the *Salmonella* preincubation test. *Mutation research*, 1983, 116:297–304.
36. Westendorf et al. Mutagenicity of naturally occurring hydroxyanthraquinones. *Mutation research*, 1990, 240:1–12.
37. Sanders D et al. Mutagenicity of crude Senna and Senna glycosides in *Salmonella typhimurium*. *Pharmacology and toxicology*, 1992, 71:165–172.

38. Lyden-Sokolowsky A, Nilsson A, Sjoberg P. Two-year carcinogenicity study with sennosides in the rat: emphasis on gastrointestinal alterations. *Pharmacology*, 1993, 47(Suppl. 1):209–215.
39. Kune GA. Laxative use not a risk for colorectal cancer: data from the Melbourne colorectal cancer study. *Zeitschrift für Gasteroenterologie*, 1993, 31:140–143.
40. Siegers CP. Anthranoid laxatives and colorectal cancer. *Trends in pharmacological sciences*, 1992, 13:229–231.
41. Lewis JH et al. The use of gastrointestinal drugs during pregnancy and lactation. *American journal of gastroenterology*, 1985, 80:912–923.
42. Beuers U, Spengler U, Pape GR. Hepatitis after chronic abuse of Senna. *Lancet*, 1991, 337:472.
43. Loew D. Pseudomelanosis coli durch Anthranoide. *Zeitschrift für Phytotherapie*, 1994, 16:312–318.
44. Müller-Lissner SA. Adverse effects of laxatives: facts and fiction. *Pharmacology*, 1993, 47(Suppl. 1):138–145.
45. Godding EW. Therapeutics of laxative agents with special reference to the anthraquinones. *Pharmacology*, 1976, 14(Suppl. 1):78–101.
46. Dufour P, Gendre P. Ultrastructure of mouse intestinal mucosa and changes observed after long term anthraquinone administration. *Gut*, 1984, 25:1358–1363.
47. Dufour P et al. Tolérance de la muqueuse intestinale de la souris à l'ingestion prolongée d'une poudre de sené. *Annales pharmaceutiques françaises*, 1983, 41:571–578.
48. Kienan JA, Heinicke EA. Sennosides do not kill myenteric neurons in the colon of the rat or mouse. *Neurosciences*, 1989, 30:837–842.
49. Riemann JF et al. Ultrastructural changes of colonic mucosa in patients with chronic laxative misuse. *Acta hepato-gastroenterology*, 1978, 25:213–218.
50. Smith BA. Effect of irritant purgatives on the myenteric plexus in man and the mouse. *Gut*, 1968, 9:139–143.
51. Riemann JF et al. The fine structure of colonic submucosal nerves in patients with chronic laxative abuse. *Scandinavian journal of gastroenterology*, 1980, 15:761–768.
52. Rieken EO et al. The effect of an anthraquinone laxative on colonic nerve tissue: a controlled trial in constipated women. *Zeitschrift für Gasteroenterologie*, 1990, 28:660–664.
53. Riemann JF, Schmidt H. Ultrastructural changes in the gut autonomic nervous system following laxative abuse and in other conditions. *Scandinavian journal of gastroenterology*, 1982, 71(Suppl.):111–124.
54. Krishnamurti S et al. Severe idiopathic constipation is associated with a distinctive abnormality of the colonic myenteric plexus. *Gastroenterology*, 1985, 88:26–34.

Radix cum Herba Taraxaci*

Definition

Radix cum Herba Taraxaci consists of the entire plant of *Taraxacum officinale* Weber ex Wiggers (Asteraceae) (*1–3*).[1]

Synonyms

For *Taraxacum officinale*: *Leontodon officinale* With., *L. taraxacum L. Taraxacum officinale* (With.) Wigg., *T. dens leonis* Desf., *T. vulgare* Schrank, (*6*).

Selected vernacular names

Ackerzichorie, amargon, blowball, Butterblume, cankerwort, capo di frate, chicoria amarga, cicoria sarvatica, cicouureya de la bonne, cicoureya deis prats, dandelion, dent-de-lion, dente di leone, dhudal, diente de leon, dhorsat al ajouz, dudhi, engraissa-porc, florion d'or, gol ghased, Gemeiner Löwenzahn, gobesag, Irish daisy, hindabaa beri, hokgei, kanphul, kanphuli, kasni sahraii, Kettenblume, khass berri, Kuhblume, lagagna, laiteron, lechuguilla, lion's tooth, Löwenzahn, maaritpauncin, marrara, milk gowan, min-deul-rre, monk's head, mourayr, mourre de por, mourre de pouerc, oduwantschiki, paardebloem, patalagagna, peirin, Pfaffendistel, Pfaffenröhrlein, Pferdeblume, pilli-pilli, piochoublit, piss-a-bed, pissa-chin, pissanliech, pissenlit, poirin, po-kong-young, porcin, pu gong ying, puffball, pugongying, Pusteblume, ringeblume, salatta merra, sanalotodo, saris berri, seiyo-tanpopo, sofione, srissi, tarakh-chaqoune, tarkhshaquin, tarassaco, taraxaco, telma retaga, Wiesenlattich, witch gowan, yellow gowan (*4–10*).

Geographical distribution

Taraxacum officinale is indigenous to the northern hemisphere (*11*). *T. mongolicum, T. sinicum* and related species are found in the Korean peninsula and China (*4, 5*).

---

* Adopted from the volume 3 of WHO monographs on selected medicinal plants.

[1] Taraxacum mongolicum Hand.-Mazz. and T. sinicum Kitag. are also recognized in the Pharmacopoeia of the People's Republic of China (4) and the *Pharmacopoeia of the Republic of Korea* (5).

Description

A perennial herb consisting of an underground, long, straight, tapering, fleshy brown root, which is continued upward as a simple or branched rhizome. From the rhizome arises a rosette of bright-green runcinate leaves and later, from the centre of the rosette, a hollow scape, 6–30 cm high bearing on its summit a broad orange-yellow head of ligulate flowers. Fruits are fusiform, greenish-brown achenes, terminating in a slender stalk crowned by a silky, spreading pappus, and borne on a globular fruiting head (*12*).

Plant material of interest: dried whole plants

General appearance

A crumpled and rolled mass. Roots conical, frequently curved, tapering, often broken into irregular pieces, externally brown. Root stock with brown or yellowish-white hairs. Leaves basal, frequently crumpled and broken; when whole, oblanceolate, greenish-brown or dark green with a pronounced midrib; apex acute or obtuse; margins lobate or pinnatifid. Pedicels one or more, each with a capitulum; involucre several rows, the inner row relatively long; corolla yellowish-brown or pale yellowish-white (*1, 4, 5*).

Organoleptic properties

Odour, slight; taste, slightly bitter (*1, 11*).

Microscopic characteristics

Epidermal cells on both leaf surfaces have sinuous anticlinal walls, cuticle striations distinct or sparsely visible. Both leaf surfaces bear non-glandular hairs with three to nine cells, 17–34 µm in diameter. Stomata, occurring more frequently on the lower surface, anomocytic or anisocytic, with three to six subsidiary cells. Mesophyll contains fine crystals of calcium oxalate. Transverse section of root shows cork with several layers of brown cells. Phloem broad, groups of laticiferous tubes arranged in several interrupted rings. Xylem relatively small, with indistinct rays, vessels large, scattered. Parenchymatous cells contain inulin (*1*).

Powdered plant material

Greenish yellow. Large root parenchymatous cells, brown reticulate vessels and tracheids and non-lignified fibres. Leaf fragments with sinuous, anticlinal-walled epidermal cells and a few anomocytic stomata. Numerous narrow annular thickened vessels and fragments of brown laticiferous tissues (*1*).

General identity tests

Macroscopic and microscopic examinations (*1*, *4*, *5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 2% (*3*).

Total ash

Not more than 17% (*3*).

Water-soluble extractive

Not less than 30% (*3*).

Loss on drying

Not more than 11% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, acid-insoluble ash, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

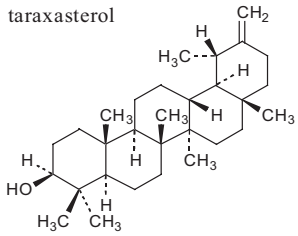
Chemical assays

To be established in accordance with national requirements.

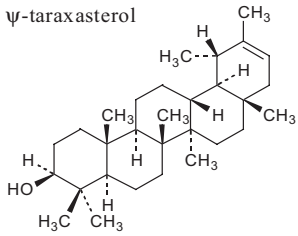
Major chemical constituents

The characteristic constituents are sesquiterpenes, including the bitter eudesmanolides tetrahydroridentin B and taraxacolide β-D-glucopyranoside; and the germacranolides, taraxinic acid β-D-glucopyranoside and 11,13-dihydrotaraxic acid β-D-glucopyranoside. Also present are the *p*-hydroxyphenylacetic acid derivative, taraxacoside; the triterpenes, taraxasterol, ψ-taraxasterol and taraxerol; and inulin (2–40%) (*4, 10, 11*). Representative structures are presented below.

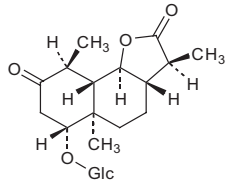
taraxasterol



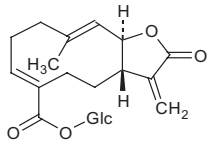
ψ-taraxasterol



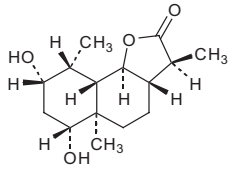
taraxacolide β-D-glucoside



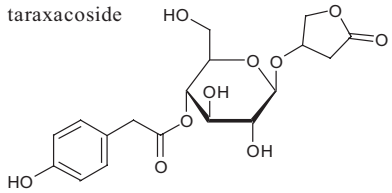
taraxinic acid β-D-glucosyl ester

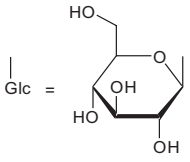


tetrahydroridentin B



taraxacoside





β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

No information available.

Uses described in pharmacopoeias and well established documents

To stimulate diuresis (*2, 5*), increase bile flow and stimulate appetite, and for treatment of dyspepsia (*2*).

Uses described in traditional medicine

As a galactagogue, laxative and tonic. Treatment of boils and sores, diabetes, fever, inflammation of the eye, insomnia, sore throat, lung abscess, jaundice, rheumatism and urinary tract infections (*10*).

Pharmacology

Experimental pharmacology

Anti-inflammatory and analgesic activity

External applications of 2.0 mg/ear of a methanol extract of the dried leaves to mice reduced ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate (*16*). Intragastric administration of 1.0 g/kg body weight (bw) of a 95% ethanol extract of the whole plant to mice inhibited benzoquinone-induced writhing (*17*). Intraperitoneal administration of 100.0 mg/kg bw of a 95% ethanol extract of the whole plant to mice inhibited carrageenan-induced footpad oedema by 42%, and reduced pain as measured by the hot-plate test and benzoquinone-induced writhing (*17*). Intragastric administration of 100.0 mg/kg bw of an 80% ethanol extract of the dried roots to rats inhibited carrageenan-induced footpad oedema by 25%, compared with 45% inhibition resulting from administration of 5.0 mg/kg bw of indometacin (*18*).

Antimicrobial activity

A 95% ethanol extract of the dried aerial parts, 1.0 mg/ml, did not inhibit the growth of *Bacillus globifer*, *B. mycoides, B. subtilis, Escherichia coli, Fusarium solani, Klebsiella pneumoniae, Penicillium notatum, Proteus morganii, Pseudomonas aeruginosa, Salmonella gallinarum, Serratia marcescens, Staphylococcus aureus, Mycobacterium smegmatis* or *Candida albicans* in vitro (*19, 20*). No antibacterial effects were observed using a 50% ethanol extract of the whole plant, 50 µl/plate, against *Escherichia coli, Salmonella enteritidis, Salmonella typhosa, Shigella dysenteriae* or *Shigella flexneri* (*21*).

Antiulcer activity

Intragastric administration of 2.0 g/kg bw of an aqueous extract of the whole plant to rats protected the animals against ethanol-induced gastric ulceration. A methanol extract, however, was not active (*22*).

Choleretic activity

Intragastric administration of an aqueous or 95% ethanol extract of the whole plant (dose not specified) to rats increased bile secretion by 40% (*23*).

Diuretic activity

Intragastric administration of 8.0–50.0 ml/kg bw of a 95% ethanol extract of the whole plant to rats induced diuresis and reduced body weight (*24*). Intragastric administration of 0.1 ml/kg bw of a 30% ethanol extract of the whole plant to mice induced diuresis (*25*). However, intragastric administration of 50.0 mg/kg bw of a chloroform, methanol or petroleum

ether extract of the roots to mice did not consistently increase urine output (*26*).

Hypoglycaemic activity

Intragastric administration of a 50% ethanol extract of the whole plant to rats, 250.0 mg/kg bw, or rabbits, 1.0 g/kg bw, reduced blood glucose concentrations (*27*). However, intragastric administration of 2.0 g/kg bw of the powdered whole plant to rabbits did not reduce blood sugar concentrations in alloxan-induced hyperglycaemia (*28*). Intragastric administration of 25.0 mg/kg bw of an aqueous extract of the dried root to mice reduced glucose-induced hyperglycaemia (*29*, *30*). However, a decoction or 80% ethanol extract of the dried roots had no effect (*30*).

Immunological effects

Intragastric administration of 3.3 g/kg bw of an aqueous extract of the whole plant to mice daily for 20 days significantly ($P < 0.01$) decreased cyclophosphamide-induced immune damage (*31*). Treatment of scalded mice with suppressed immune functions with an aqueous extract of the whole plant (dose and route not specified) stimulated the immune response (*32*). Nitric oxide synthesis inhibition induced by cadmium in mouse peritoneal macrophages stimulated with recombinant interferon-γ and lipopolysaccharide was counteracted by treatment of the cells with an aqueous extract of the whole plant, 100 µg/ml. The results were mainly dependent on the induction of tumour necrosis factor-α (TNF-α) secretion stimulated by the aqueous extract (*33*). Treatment of primary cultures of rat astrocytes with an aqueous extract of the whole plant, 100.0 µg/ml, inhibited TNF-α production induced by lipopolysaccharide and substance P. The treatment also decreased the production of interleukin-1 in astrocytes stimulated with lipopolysaccharide and substance P. The study indicated that Radix cum Herba Taraxaci may inhibit TNF-α production by inhibiting interleukin-1 production, thereby producing anti-inflammatory effects (*34*). Treatment of mouse peritoneal macrophages with an aqueous extract of the whole plant, 100 µg/ml, after treatment of the cells with recombinant interferon-γ, resulted in increased nitric oxide synthesis owing to an increase in the concentration of inducible nitric oxide synthase. The results were dependent on the induction of TNF-α secretion by Radix cum Herba Taraxaci (*35*).

Toxicology

The intraperitoneal median lethal dose (LD_{50}) of a 95% ethanol extract of the whole plant in rats was 28.8 mg/kg bw (*24*). In rats, the maximum tolerated dose of a 50% ethanol extract of the whole plant administered by the

intraperitoneal route was 500.0 mg/kg bw (*27*). No visible signs of toxicity were observed in rabbits after intragastric administration of the powdered whole plant at doses of 3–6 g/kg bw per day for up to 7 days (*36*).

Clinical pharmacology

No information available.

Adverse reactions

Allergic reactions including anaphylaxis and pseudoallergic contact dermatitis have been reported (*37–40*). Cross-reactivity has been reported in individuals with an allergy to the pollen of other members of the Asteraceae (*41*).

Contraindications

Radix cum Herba Taraxaci is contraindicated in obstruction of the biliary or intestinal tract, and acute gallbladder inflammation. In case of gallbladder disease, Radix cum Herba Taraxacum should only be used under the supervision of a health-care professional (*2*).

Warnings

May cause stomach hyperacidity, as with all drugs containing amaroids (*2*).

Precautions

Drug interactions

A decrease in the maximum plasma concentration of ciprofloxacin was observed in rats treated with concomitant oral administration of 2.0 g/kg bw of an aqueous extract of the whole plant and 20.0 mg/kg bw of ciprofloxacin (*42*).

Carcinogenesis, mutagenesis, impairment of fertility

No effects on fertility were observed in female rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (*43*).

Pregnancy: teratogenic effects

No teratogenic or embryotoxic effects were observed in the offspring of rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (*43*).

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried whole plant, native dry extract, fluidextract and tincture (*1, 2*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose: 3–4 g of cut or powdered whole plant three times; decoction, boil 3–4 g of whole plant in 150 ml of water; infusion, steep 1 tablespoonful of whole plant in 150 ml of water; 0.75–1.0 g of native dry extract 4:1 (w/w); 3–4 ml fluidextract 1:1 (g/ml) (*2*); 5–10 ml of tincture (1:5 in 45% alcohol) three times (*1*).

References

1. *British herbal pharmacopoeia*. Exeter, British Herbal Medicine Association, 1996.
2. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
3. *Deutscher Arzneimittel-Codex*. [German drug codex.] Stuttgart, Deutsche Apotheker, 1998.
4. *Pharmacopoeia of the People's Republic of China (English edition). Vol. I.* Beijing, China, Chemical Industry Press, 2000.
5. *Pharmacopoeia of the Republic of Korea*, 7th ed. Seoul, Taechan yakjon, 1998.
6. Hänsel R et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Bd 6, Drogen P–Z*, 5th ed. [Hager's handbook of pharmaceutical practice. Vol. 6, Drugs P–Z, 5th ed.] Berlin, Springer, 1994.
7. Zahedi E. *Botanical dictionary. Scientific names of plants in English, French, German, Arabic and Persian languages*. Tehran, Tehran University Publications, 1959.
8. Issa A. *Dictionnaire des noms des plantes en latin, français, anglais et arabe*. [Dictionary of plant names in Latin, French, English and Arabic.] Beirut, Dar al-Raed al-Arabi, 1991.
9. *Medicinal plants in the Republic of Korea.* Manila, Philippines, World Health Organization Regional Office for the Western Pacific, 1998 (WHO Regional Publications, Western Pacific Series, No. 21).
10. Farnsworth NR, ed. *NAPRALERT database.* Chicago, IL, University of Illinois at Chicago, 9 February 2001 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
11. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
12. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, PA, Blakiston, 1950.

13. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
14. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
15. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (WHO/FSF/FOS/97.7; available from Food Safety, World Health Organization, 1211 Geneva 27, Switzerland).
16. Yasukawa K et al. Inhibitory effect of edible plant extracts on 12-*O*-tetradecanoylphorbol-13-acetate-induced ear oedema in mice. *Phytotherapy Research*, 1993, 7:185–189.
17. Tita B et al. *Taraxacum officinale* W.: Pharmacological effect of an ethanol extract. *Pharmacology Research*, 1993, 27(Suppl. 1):23–24.
18. Mascolo N et al. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytotherapy Research*, 1987, 1:28–31.
19. Mitscher LA et al. Antimicrobial agents from higher plants. I. Introduction, rationale, and methodology. *Lloydia*, 1972, 35:157–166.
20. Recio MC, Ríos JL, Villar A. Antimicrobial activity of selected plants employed in the Spanish Mediterranean area. Part II. *Phytotherapy Research*, 1989, 3:77–80.
21. Caceres A, Cano O, Samayoa B et al. Plants used in Guatemala for the treatment of gastrointestinal disorders. 1. Screening of 84 plants against enterobacteria. *Journal of Ethnopharmacology*, 1990, 30:55–73.
22. Muto Y et al. [Studies on antiulcer agents. I. The effects of various methanol and aqueous extracts of crude drugs on antiulcer activity.] *Yakugaku Zasshi*, 1994, 114:980–994 [in Japanese].
23. Böhm K. Untersuchungen über choleretische Wirkungen einiger Arzneipflanzen. [Studies on the choleretic action of some medicinal plants.] *Arzneimittelforschung*, 1959, 9:376–378.
24. Racz-Kotilla E, Racz G, Solomon A. The action of *Taraxacum officinale* extracts on the body weight and diuresis of laboratory animals. *Planta Medica*, 1974, 26:212–217.
25. Leslie GB. A pharmacometric evaluation of nine Bio-Strath herbal remedies. *Medita*, 1978, 8:3–19.
26. Hook I, McGee A, Henman M. Evaluation of dandelion for diuretic activity and variation in potassium content. *International Journal of Pharmacognosy*, 1993, 31:29–34.
27. Dhar ML et al. Screening of Indian plants for biological activity: part 1. *Indian Journal of Experimental Biology*, 1968, 6:232–247.
28. Akhtar MS, Khan QM, Khaliq T. Effects of *Portulaca oleracae* (kulfa) and *Taraxacum officinale* (dhudhal) in normoglycaemic and alloxan-treated hyperglycaemic rabbits. *Journal of the Pakistan Medical Association*, 1985, 35:207–210.

29. Neef H, DeClercq P, Laekeman G. Hypoglycemic activity of selected European plants. *Pharmacy World and Science*, 1993, 15:H11.
30. Neef H, DeClercq P, Laekeman G. Hypoglycemic activity of selected European plants. *Phytotherapy Research*, 1995, 9:45–48.
31. Hong Y et al. [The effect of *Taraxacum mongolicum* on immune function in mouse.] *Journal of Guiyang Medical College*, 1997, 22:137–139 [in Chinese].
32. Luo ZH. [The use of Chinese traditional medicines to improve impaired immune functions in scald mice.] *Chung Hua Cheng Hsing Shao Shang Wai Ko Tsa Chih*, 1993, 9:56–58 [in Chinese].
33. Kim HM et al. *Taraxacum officinale* restores inhibition of nitric oxide production by cadmium in mouse peritoneal macrophages. *Immunopharmacology and Immunotoxicology*, 1998, 20:283–297.
34. Kim HM et al. *Taraxacum officinale* inhibits tumor necrosis factor-alpha production from rat astrocytes. *Immunopharmacology and Immunotoxicology*, 2000, 22:519–530.
35. Kim HM, Oh CH, Chung CK. Activation of inducible nitric oxide synthase by *Taraxacum officinale* in mouse peritoneal macrophages. *General Pharmacology*, 1999, 32:683–688.
36. Akhtar MS. Hypoglycemic activities of some indigenous medicinal plants traditionally used as antidiabetic drugs. *Journal of the Pakistan Medical Association*, 1992, 42:271–277.
37. Lovell CR, Rowan M. Dandelion dermatitis. *Contact Dermatitis*, 1991, 25:185–188.
38. Chivato T et al. Anaphylaxis induced by ingestion of a pollen compound. *Journal of Investigational Allergology and Clinical Immunology*, 1996, 6:208–209.
39. Dawe RS et al. Daisy, dandelion and thistle contact allergy in the photosensitivity dermatitis and actinic reticuloid syndrome. *Contact Dermatitis*, 1996, 32:109–110.
40. Mark KA et al. Allergic contact and photoallergic contact dermatitis to plant and pesticide allergens. *Archives of Dermatology*, 1999, 135:67–70.
41. Fernandez C et al. Analysis of cross-reactivity between sunflower pollen and other pollens of the Compositae family. *Journal of Allergy and Clinical Immunology*, 1993, 92:660–667.
42. Zhu M, Wong PY, Li RC. Effects of *Taraxacum mongolicum* on the bioavailability and disposition of ciprofloxacin in rats. *Journal of Pharmaceutical Sciences*, 1999, 88:632–634.
43. Leslie GB, Salmon G. Repeated dose toxicity studies and reproductive studies on nine Bio-Strath herbal remedies. *Schweizerische Zeitschrift für Medizin und Medizinische Technik*, 1979, 1:1–3.

Herba Thymi*

Definition

Herba Thymi is the dried leaves and flowering tops of *Thymus vulgaris* L. or of *Thymus zygis* L. (Lamiaceae) (*1*, *2*).

Synonyms

Lamiaceae are also known as Labiatae.

Selected vernacular names

Common thyme, farigola, garden thyme, herba timi, herba thymi, mother of thyme, red thyme, rubbed thyme, ten, thick leaf thyme, thym, Thymian, thyme, time, timi, tomillo, za'ater (*1*, *3–7*).

Description

An aromatic perennial sub-shrub, 20–30 cm in height, with ascending, quadrangular, greyish brown to purplish brown lignified and twisted stems bearing oblong-lanceolate to ovate-lanceolate greyish green leaves that are pubescent on the lower surface. The flowers have a pubescent calyx and a bilobate, pinkish or whitish, corolla and are borne in verticillasters. The fruit consists of 4 brown ovoid nutlets (*5*, *8*, *9*).

Plant material of interest: dried leaves and flowering tops

General appearance

Thymus vulgaris

Leaf 4–12 mm long and up to 3 mm wide; it is sessile or has a very short petiole. The lamina is tough, entire, lanceolate to ovate, covered on both surfaces by a grey to greenish grey indumentum; the edges are markedly rolled up towards the abaxial surface. The midrib is depressed on the adaxial surface and is very prominent on the abaxial surface. The calyx is green, often with violet spots, and is tubular; at the end are 2 lips of which the upper is bent back and has 3 lobes on its end; the lower is longer and

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.

has 2 hairy teeth. After flowering, the calyx tube is closed by a crown of long, stiff hairs. The corolla, about twice as long as the calyx, is usually brownish in the dry state and is slightly bilabiate (*1*).

Thymus zygis

Leaf 1.7–6.5 mm long and 0.4–1.2 mm wide; it is acicular to linear-lanceolate and the edges are markedly rolled toward the abaxial surface. Both surfaces of the lamina are green to greenish grey and the midrib is sometimes violet; the edges, in particular at the base, have long, white hairs. The dried flowers are very similar to those of *Thymus vulgaris* (*1*).

Organoleptic properties

Odour and taste aromatic (*1–3*, *5*).

Microscopic characteristics

In leaf upper epidermis, cells tangentially elongated in transverse section with a thick cuticle and few stomata, somewhat polygonal in surface section with beaded vertical walls and striated cuticle, the stoma being at a right angle to the 2 parallel neighbouring cells. Numerous unicellular, non-glandular hairs up to 30 µm in length with papillose wall and apical cell, straight, or pointed, curved, or hooked. Numerous glandular hairs of two kinds, one with a short stalk embedded in the epidermal layer and a unicellular head, the other with an 8- to 12-celled head and no stalk. Palisade parenchyma of 2 layers of columnar cells containing many chloroplastids; occasionally an interrupted third layer is present. Spongy parenchyma of about 6 layers of irregular-shaped chlorenchyma cells and intercellular air-spaces (*5*).

Powdered plant material

Grey-green to greenish brown powder; leaf fragments, epidermal cells prolonged into unicellular pointed, papillose trichomes, 60 µm long; trichomes of the lower surface uniseriate, 2–3 celled, sharp pointed, up to 300 µm in diameter, numerous labiate trichomes with 8–12 secretory cells up to 80 µm in diameter; broadly elliptical caryophyllaceous stomata. Six- to 8-celled uniseriate trichomes from the calyx up to 400 µm long; pollen grains spherical; pericyclic fibres of the stem (*1–3*).

Geographical distribution

Indigenous to southern Europe. It is a pan-European species that is cultivated in Europe, the United States of America and other parts of the world (*2*, *3*, *5*, *10*).

General identity tests

Macroscopic and microscopic examinations (*1, 5*), and chemical and thin-layer chromatography tests for the characteristic volatile oil constituent, thymol [**1**].

Purity tests

Microbiology

The test for *Salmonella* spp. in Herba Thymi products should be negative. The maximum acceptable limits of other microorganisms are as follows (*11–13*). For preparation of infusion: aerobic bacteria—not more than 10^7/g; fungi—not more than 10^5/g; *Escherichia coli*–not more than 10^2/g. Preparations for oral use: aerobic bacteria—not more than 10^5/ml; fungi—not more than 10^4/ml; enterobacteria and certain Gram-negative bacteria—not more than 10^3/ml; *Escherichia coli*—0/ml.

Foreign organic matter

Not more than 10% of stem having a diameter up to 1 mm. Leaves with long trichomes at their base and with weakly pubescent other parts not allowed (*1*). The leaves and flowering tops of *Origanum creticum* or *O. dictamnus* are considered adulterants (*3*, *5*). Other foreign organic matter, not more than 2% (*2*).

Total ash

Not more than 15% (*1*).

Acid-insoluble ash

Not more than 2.0% (*1*).

Moisture

Not more than 10% (*1*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Herba Thymi is not more than 0.05 mg/kg (*13*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*11*) and guidelines for predicting dietary intake of pesticide residues (*14*).

Heavy metals

Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*11*).

Radioactive residues

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*11*).

Other purity tests

Chemical, alcohol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

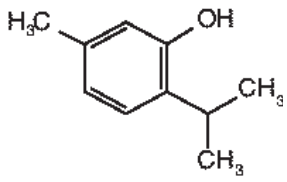
Chemical assays

Herba Thymi contains not less than 1.0% volatile oil (*2*, *3*), and not less than 0.5% phenols. Volatile oil is quantitatively determined by water/steam distillation (*1*), and the percentage content of phenols expressed as thymol is determined by spectrophotometric analysis (*1*). Thin-layer chromatographic analysis is used for thymol, carvacrol, and linalool (*1*, *15*).

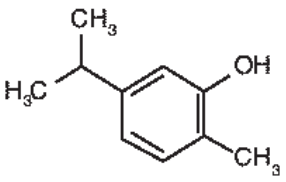
Major chemical constituents

Herba Thymi contains about 2.5% but not less than 1.0% of volatile oil. The composition of the volatile oil fluctuates depending on the chemotype under consideration. The principal components of Herba Thymi are thymol [**1**] and carvacrol [**2**] (up to 64% of oil), along with linalool, *p*-cymol, cymene, thymene, α-pinene, apigenin, luteolin, and 6-hydroxyluteolin glycosides, as well as di-, tri- and tetramethoxylated flavones, all substituted in the 6-position (for example 5,4'-dihydroxy-6,7-dimethoxyflavone, 5,4'-dihydroxy-6,7,3'-trimethoxyflavone and its 8-methoxylated derivative 5,6,4'-trihydroxy-7,8,3'-trimethoxyflavone) (*1*, *3–6*, *9*).

thymol **[1]**



carvacrol **[2]**



Dosage forms

Dried herb for infusion, extract, and tincture (*1*).

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and in traditional systems of medicine

Thyme extract has been used orally to treat dyspepsia and other gastrointestinal disturbances; coughs due to colds, bronchitis and pertussis; and laryngitis and tonsillitis (as a gargle). Topical applications of thyme extract have been used in the treatment of minor wounds, the common cold, disorders of the oral cavity, and as an antibacterial agent in oral hygiene (*3*, *5*, *8*, *15*, *16*). Both the essential oil and thymol are ingredients of a number of proprietary drugs including antiseptic and healing ointments, syrups for the treatment of respiratory disorders, and preparations for inhalation. Another species in the genus, *T. serpyllum* L., is used for the same indications (*8*).

Uses described in folk medicine, not supported by experimental or clinical data

As an emmenagogue, sedative, antiseptic, antipyretic, to control menstruation and cramps, and in the treatment of dermatitis (*7*).

Pharmacology

Experimental pharmacology

Spasmolytic and antitussive activities

The spasmolytic and antitussive activity of thyme has been most often attributed to the phenolic constituents thymol and carvacrol, which make up a large percentage of the volatile oil (*17*). Although these compounds have been shown to prevent contractions induced in the ileum and the trachea of the guinea-pig, by histamine, acetylcholine and other reagents, the concentration of phenolics in aqueous preparations of the drug is insufficient to account for this activity (*18*, *19*). Experimental evidence suggests that the in vitro spasmolytic activity of thyme preparations is due to the presence of polymethoxyflavones (*10*). In vitro studies have shown that flavones and thyme extracts inhibit responses to agonists of specific receptors such as acetylcholine, histamine and l-norepinephrine, as well as agents whose actions do not require specific receptors, such as barium chloride (*10*). The flavones of thyme were found to act as non-competitive and non-specific antagonists (*10*); they were also shown to be Ca^{2+} antagonists and musculotropic agents that act directly on smooth muscle (*10*).

Expectorant and secretomotor activities

Experimental evidence suggests that thyme oil has secretomotoric activity (*20*). This activity has been associated with a saponin extract from

T. vulgaris (*21*). Stimulation of ciliary movements in the pharynx mucosa of frogs treated with diluted solutions of thyme oil, thymol or carvacrol has also been reported (*22*). Furthermore, an increase in mucus secretion of the bronchi after treatment with thyme extracts has been observed (*23*).

Antifungal and antibacterial activities

In vitro studies have shown that both thyme essential oil and thymol have antifungal activity against a number of fungi, including *Cryptococcus neoformans*, *Aspergillus*, *Saprolegnia*, and *Zygorhynchus* species (*24–27*). Both the essential oil and thymol had antibacterial activity against *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, and a number of other bacterial species (*28*, *29*). As an antibiotic, thymol is 25 times as effective as phenol, but less toxic (*30*).

Contraindications

Pregnancy and lactation (See Precautions, below).

Warnings

No information available.

Precautions

General

Patients with a known sensitivity to plants in the Lamiaceae (Labiatae) should contact their physician before using thyme preparations. Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

Thyme essential oil did not have any mutagenic activity in the *Bacillus subtilis rec*-assay or the *Salmonella*/microsome reversion assay (*32*, *33*). Recent investigations suggest that thyme extracts are antimutagenic (*34*) and that luteolin, a constituent of thyme, is a strong antimutagen against the dietary carcinogen Trp-P-2 (*35*).

Pregnancy: non-teratogenic effects

The safety of Herba Thymi preparations during pregnancy or lactation has not been established. As a precautionary measure, the drug should not be used during pregnancy or lactation except on medical advice. However, widespread use of Herba Thymi has not resulted in any safety concerns.

Nursing mothers

See Pregnancy: non-teratogenic effects, above.

Other precautions

No information available concerning drug interactions, drug and laboratory test interactions, paediatric use, or teratogenic effects on pregnancy.

Adverse reactions

Contact dermatitis has been reported. Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (*31*).

Posology

Adults and children from 1 year: 1–2 g of the dried herb or the equivalent amount of fresh herb as an oral infusion several times a day (*30*, *36*); children up to 1 year: 0.5–1 g (*36*). Fluid extract: dosage calculated according to the dosage of the herb (*37*). Tincture (1:10, 70% ethanol): 40 drops up to 3 times daily (*38*). Topical use: a 5% infusion as a gargle or mouth-wash (*30*, *38*).

References

1. *European pharmacopoeia*, 2nd ed. Strasbourg, Council of Europe, 1995.
2. *Materia medika Indonesia*, Jilid. Jakarta, IV Departemen Kesehatan, Republik Indonesia, 1980.
3. *British herbal phamacopoeia*, Part 2. London, British Herbal Medicine Association, 1979.
4. *Deutsches Arzneibuch 1996*. Stuttgart, Deutscher Apotheker Verlag, 1996.
5. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, Blakiston, 1950.
6. Ghazanfar SA. *Handbook of Arabian medicinal plants.* Boca Raton, FL, CRC Press, 1994:128.
7. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, March 15, 1995 production (an on-line database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
8. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
9. Mossa JS, Al-Yahya MA, Al-Meshal IA. *Medicinal plants of Saudi Arabia*, *Vol. 1*. Riyadh, Saudi Arabia, King Saud University Libraries, 1987.
10. Van den Broucke CO, Lemli JA. Spasmolytic activity of the flavonoids from *Thymus vulgaris. Pharmaceutisch Weekblad, scientific edition*, 1983, 5:9–14.
11. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.

12. *Deutsches Arzneibuch 1996. Vol. 2. Methoden der Biologie*. Stuttgart, Deutscher Apotheker Verlag, 1996.
13. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1997.
14. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (unpublished document WHO/FSF/FOS/97.7; available from Food Safety, WHO, 1211 Geneva 27, Switzerland).
15. Twetman S, Hallgren A, Petersson LG. Effect of antibacterial varnish on mutans *Streptococci* in plaque from enamel adjacent to orthodontic appliances. *Caries research*, 1995, 29:188–191.
16. Petersson LG, Edwardsson S, Arends J. Antimicrobial effect of a dental varnish, in vitro. *Swedish dental journal*, 1992, 16:183–189.
17. Reiter M, Brandt W. Relaxant effects on tracheal and ileal smooth muscles of the guinea pig. *Arzneimittel-Forschung*, 1985, 35:408–414.
18. Van Den Broucke CO. Chemical and pharmacological investigation on Thymi herba and its liquid extracts. *Planta medica*, 1980, 39:253–254.
19. Van Den Broucke CO, Lemli JA. Pharmacological and chemical investigation of thyme liquid extracts. *Planta medica*, 1981, 41:129–135.
20. Gordonoff T, Merz H. Über den Nachweis der Wirkung der Expektorantien. *Klinische Wochenschrift*, 1931, 10:928–932.
21. Vollmer H. Untersuchungen über Expektorantien und den Mechanismus ihrer Wirkung. *Klinische Wochenschrift*, 1932, 11:590–595.
22. Freytag A. Über den Einfluß von Thymianöl, Thymol und Carvacrol auf die Flimmerbewegung. *Pflügers Archiv, European journal of physiology*, 1933, 232:346–350.
23. Schilf F. Einfluss von Azetylcholin, Adrenalin, Histamin und Thymianextrakt auf die Bronchialschleimhautsekretion; zugleich ein Beitrag zur Messung der Bronchialschleimhautsekretion. *Naunyn-Schmiedebergs Archiv für Pharmakologie,* 1932, 166:22–25.
24. Vollon C, Chaumont JP. Antifungal properties of essential oils and their main components upon *Cryptococcus neoformans*. *Mycopathology*, 1994, 128:151–153.
25. Perrucci S et al. In vitro antimycotic activity of some natural products against *Saprolegnia ferax*. *Phytotherapy research*, 1995, 9:147–149.
26. Pasteur N et al. Antifungal activity of oregano and thyme essential oils applied as fumigants against fungi attacking stored grain. *Journal of food protection*, 1995, 58:81–85.
27. Tantaouielaraki A, Errifi A. Antifungal activity of essential oils when associated with sodium chloride or fatty acids. *Grasas-y-aceites*, 1994, 45:363–369.
28. Janssen AM, Scheffer JJC, Baerheim-Svendsen A. Antimicrobial activity of essential oils: A 1976–1986 literature review. Aspects of the test methods. *Planta medica*, 1987, 53:395–398.

29. Juven BJ, Kanner J, Schved F, Weisslowicz H. Factors that interact with the antibacterial action of thyme essential oil and its active constituents. *Journal of applied bacteriology*, 1994, 76:626–631.
30. Czygan C-F. Thymian, Thymi Herba. In: Wichtl M. ed. *Teedrogen*, 2nd ed. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1989:498–500.
31. Wüthrich B, Stäger P, Johannson SGO. Rast-specific IGE against spices in patients sensitized against birch pollen, mugwort pollen and celery. *Allergologie*, 1992, 15:380–383.
32. Zani F et al. Studies on the genotoxic properties of essential oils with *Bacillus subtilis* rec-assay and *Salmonella*/microsome reversion assay. *Planta medica*, 1991, 57:237–241.
33. Azizan A, Blevins RD. Mutagenicity and antimutagenicity testing of six chemicals associated with the pungent properties of specific spices as revealed by the Ames *Salmonella* microsomal assay. *Archives of environmental contamination and toxicology*, 1995, 28:248–258.
34. Natake M et al. Herb water-extracts markedly suppress the mutagenicity of Trp-P-2. *Agricultural and biological chemistry*, 1989, 53:1423–1425.
35. Samejima K et al. Luteolin, a strong antimutagen against dietary carcinogen, Trp-P-2, in peppermint, sage, and thyme. *Journal of agricultural and food chemistry*, 1995, 43:410–414.
36. Dorsch W et al. In: *Empfehlungen zu Kinderdosierungen von monographierten Arzneidrogen und ihren Zubereitungen*. Bonn, Kooperation Phytopharmaka, 1993:100–101.
37. Hochsinger K. Die Therapie des Krampf- und Reizhustens. *Wiener Medizinische Wochenschrift*, 1931, 13:447–448.
38. Van Hellemont J. *Fytotherapeutisch compendium*, 2nd ed. Bonn, Scheltema & Holkema, 1988:599–605.

Flos Tiliae

Definition

Flos Tiliae consists of the whole or cut dried inflorescence of wild or cultivated *Tilia cordata* Mill. and *Tilia platyphyllos* Scop. (Tiliaceae) collected during the flowering phase (*1*).

Note: According to the *European Pharmacopoeia*, Flos Tiliae consists of the whole, dried inflorescences of *Tilia cordata* Miller, of *Tilia platyphyllos* Scop., of *Tilia x vulgaris* Heyne or a mixture of these (Tiliaceae) (*2*). They are usually supplied whole, but the materials used for commercial purposes may be broken up (*3*).

Synonyms

T. cordata: *T. europaea* var. γ L., *T. parvifolia* Ehrl., *T. microphylla* Vent., *T. microphylla* Willd., *T. ulmifolia* Scop., *T. silvestris Scop., T. platyphyllos*, *T. cordifolia* Bess., *T. europaea* var. β L., *T. grandifolia* (Ehrh.), *T. pauciflora* Heyne (*4*, *5*).

Selected vernacular names

Both species: Bastbaum, lime, Linde, linden, linden flowers, Lindenbluten, tilia.

Tiilia cordata: bass, bass-tree, bast-tree, common lime, drebnolistnaja lipa, English lime, European lime, European linden, European small-leaf lime, European small-leaf limetree, European small-leaf linden, europees linden, europeisk lind, harilik pärn, kislevelu hars, kleinbladige linde, kleinblättrige linde, lehmus, lime, limetree, lime-tree, lind, linde, linden, littleleaf linden, lipa malolistna, lipa melkolistnaya, lipa serdtsevidnaya, locust-bloom, maida gulli zhuka, malolista, melkolistnaya lipa, niinipuu, parastā liepa, parklind, shinanoki, sinanoki, skogs-lind, small-leaved linden, sommerlinde, steinlinde, spätlinde, steinlinde, tei pădureţ, tei pucios, tei roşu, tei cu frunza mică, tiel-tree, tiglio, tiglio a foglie, tiglio selvatico, tilleau sauvage, tilleul, tilleul a petites feuilles, tilleul des bois, tilleul feuilles, tilleul sauvage, tilo, tilo silvestre, tilleul a petites feuilles, til-tree, waldlinde, winterlinde, winter-linde, zvilpotola cachvi.

Tilia platyphyllos: bigleaf linden, broad-leaved lime, fleur de tilluel, Frühlinde, Graslinde, Grossblättrige Linde, large-leaved linden, lehmus, lipa, krupnolistnaja, lipa ploskolistnaja, mshvilpotola cachvi, platlapu liepa, sommerlinde, storblading lind, summer linden, suurelehine pärn, tei mare, tei cu frunza mare, tilleul à grandes feuilles (*6–15*).

Geographical distribution

Indigenous throughout Europe. It is common in northern temperate regions of the world and is also cultivated (*6*, *7*, *16–22*).

Description

Tilia cordata. Medium-sized trees, about 20 m high; wide spreading root system; crown, strikingly dense pyramidal when young, becoming rounded when mature; bark grey to brown, ridged and furrowed on older trees. (*T. platyphyllos* is about 30–40 m high, the branches are thicker and less dense.) Buds: lateral buds alternate, no terminal buds, two shiny glabrous bud-scales, reddish-brown or yellowish-brown, up to 6 mm long and 4 mm wide. (*T. platyphyllos* has hairy non-shiny buds, covered by three bud-scales.) Leaves: simple, cordate, oblique or cordate base, finely serrate, dentate or bidentate, palmate; veinlets of third order non-parallel; glabrous and slightly lustrous above, glabrous beneath with axillary tufts of brown hairs, 2–8(12) cm long, 2–6(10) cm wide, dark green above, bluish-green beneath; petiole 2.5–4.5 cm long. Upper branches fertile, lower ones sterile. The leaves of sterile branches are bigger and darker. (*T. platyphyllos* leaves have axillary tufts of white hairs, 5–8(17) cm long, 6–9(19) cm wide, dark green above, pale green beneath, with prominent parallel veinlets of third order.) Inflorescence: 5–15 flowered horizontal or erect cymes, bearing pale greenish-yellow, leaf-like bracts; bract as long as inflorescence, about 6 cm long, 1–1.5 cm wide; petiole 3–7 cm long. (*T. platyphyllos* has 2–7-flowered pendulous cymes, the bracts are shorter than the inflorescence, 5–9 cm long, up to 2.5 cm wide.) Flower: actinomorphous, hermaphrodite, pentamerous; petals greenish-yellow to pale yellow; stamens, about 30, no staminodes; ovary, pubescent, superior, 5-locular with one smooth style, 5 stigmas; scented, geniculate peduncles are between 1.5 and 3 cm long. (*T. platyphyllos* flowers 10–15 days before *T. cordata*.) Fruits: nutlets, spherical, without ribs, thin shelled, 4–6 mm in diameter, brown to tan when mature (*T. platyphyllos* has oval or pear-shaped nutlets, with woody shell and 3–5 ridges, tomentose, cream-coloured, up to 1 cm in diameter) (*6*, *23–30*).

Plant material of interest: dried inflorescences

General appearance

The inflorescence is yellowish-green. The main axis of the inflorescence bears a linguiform bract, membranous, yellowish-green, practically glabrous, the central vein of which is joined to about half its length with the peduncle. Flowers are arranged in clusters of 3–7 on a stalked pendulous cyme (*T. platyphyllos*) or in clusters of 3–15 on a stalked erect cyme (*T. cordata*). The diameter of the flowers is between 1 and 1.5 cm. Sepals are easily detached, oblong-ovate, greyish-green, up to 6 mm long; their abaxial surface is usually glabrous, their adaxial surface and their borders are strongly pubescent. The 5 spatulate or ovate, thin petals are yellowish-white, up to 8 mm long. They show fine venation and their borders are only sometimes covered with isolated trichomes. The numerous stamens are free and usually constitute 5 groups. The superior ovary has a pistil with a 5-lobate stigma. The fruits are nutlets, 2 mm in diameter. The cut drug consists of fragments of inflorescences with a diameter 0.5–20 mm (*1–3*).

Organoleptic properties

Odour: faint aromatic, characteristic; taste: faint, aromatic, sweetish and mucilaginous (*1–3*).

Microscopic characteristics

The adaxial epidermis of the bract has cells with straight or slightly sinuous anticlinal walls. The abaxial epidermis has cells with wavy-sinuous anticlinal walls and anomocytic stomata. Two types of trichomes occur near the junction of the bract vein with the peduncle: one glandular, with short 1–3-cellular stalk, and oval multicellular head, and the other covering, stellate, with 3–7 long sinuous cells. The mesophyll is spongious, with clusters or prismatic crystals of calcium oxalate. The parenchyma of the sepals, particularly near the veins, has numerous mucilaginous cells and cells containing small calcium oxalate clusters. The adaxial epidermis of sepals has bent, thick-walled covering trichomes, unicellular or stellate with up to 5 cells. The epidermal cells of the petals have straight anticlinal walls with a striated cuticle without stomata. The parenchyma of the petals contains small calcium oxalate clusters (8–16 µm in diameter) and mucilaginous cells. The mucilage stains pink with ruthenium red solution. The pollen grains have a diameter of about 30–40 µm and are oval or slightly angular with 3 germinal pores and a finely granulated exine. The ovary is glabrous or densely covered with trichomes, often very twisted, unicellular with 2–4 branches. The diagnostic features include the sclereids of the bracts and the tufted trichomes of the sepals, as well as the stel-

late trichomes of the ovary (*1–3*, *31*). According to the *Österreichisches Arzneibuch* (*32*) and *Pharmacopoeia Helvetica* VII (*33*), adulterants can be recognized microscopically by the densely pubescent bracts (e.g. *T. americana* L. and *T. tomentosa* Moench), and/or by the flowers having petalaceous staminodes (e.g. *T. tomentosa*).

Powdered plant material

Pale green powder; lower epidermis of bract has sinuous anticlinal walls, striated cuticle, anomocytic stomata, stellate trichomes and glandular trichomes; epidermal cells of petals elongated, straight anticlinal walls; mesophyll with large cells containing mucilage which stains pink with ruthenium red solution; cluster crystals of calcium oxalate; tetragonal pollen grains with finely warty exine (*3*).

General identity tests

Macroscopic and microscopic examinations, thin-layer chromatography for the presence of rutin, hyperoside, caffeic acid and other characteristic constituents (*2*), and colour reaction of the cut drug with 5% ammonia solution for the detection of flavonoids. If the cut drug is soaked for 3–5 minutes in cold water, the fragments of drug are mucilaginous to the touch (*1*). The mesophyll has large cells containing mucilage, which stain pink with ruthenium red solution (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*34*).

Chemical

To be established according to national requirements. The German pharmacopoeia (*35*) describes identification by detection of the flavonoids using the Shinoda reaction, and also by separation by thin-layer chromatography (*6*).

Foreign organic matter

Not more than 2% (*2*, *3*). There should be no inflorescences with a bract bearing at the abaxial face stellate, 5–8-rayed trichomes and flowers having an apparent double corolla by transformation of 5 stamens into petal-like staminoids and having a pistil which is not lobular nor indented. Hexamer-

ous flowers occur only occasionally (*T. americana* L., *T. tomentosa* Moench) (*2*). Not more than 0.3% of organic matter. Not more than 2% of inflorescences with bract or of bracts without inflorescences which have been damaged by insects or harmed by erysiphe. Brownish and blackish fragments of inflorescences, not more than 4%. Not more than 1% of other parts of plant (leaves and branches). Not more than 2% of inflorescences with fruits. For whole drug: not more than 3% of fragments of drug having a diameter less than 3 mm; not more than 15% of fragments of drug spilled from flowers or from inflorescences without bract. For cut drug: not more than 10% of fragments of drug having a diameter less than 0.310 mm (*1*).

Total ash
Not more than 8% (*2*).

Acid-insoluble ash
Not more than 4% of ash insoluble in hydrochloric acid (*3*).

Sulfated ash
Not more than 10% (*33*).

Water-soluble extractive
Not less than 10% (*36*).

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 12% (*2*). Not more than 13% (*1*).

Swelling index
Not less than 15 (*33*).

Pesticide residues
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*2*). For other pesticides, see the *European pharmacopoeia* (*2*) and the WHO guidelines on quality control methods for medicinal plant materials (*34*) and pesticide residues (*37*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*34*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*34*) for the analysis of radioactive isotopes.

Other purity tests

The content of mineral matter should be not more than 0.1% (*1*). Chemical and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

To be established in accordance with national requirements.

Major chemical constituents

The major constituents of the dried inflorescences are flavonoids (1–5%): chiefly quercetin glycosides (rutin, hyperoside, quercitrin and 3-glucosyl-7-rhamnoside), and kaempferol glucosides (astragalin (kaempferol-3-glucoside), tiliroside (astragalin-6˝-*p*-coumaroylester), astragalin-3-glucosyl-7-rhamnoside, astragalin-3,7-dirhamnoside). A complex of mucilage (7–10%, particularly from the bracts, mainly arabino-galactans with some uronic acid units) is present. The mucilage is composed of 5 fractions dominated by D-galactose, L-arabinose, L-rhamnose and uronic acid, with smaller amounts of glucose, mannose and xylose. The essential oil (0.02–0.1%) contains farnesol and its acetate, linalool, geraniol, geranyl acetate, germacrene, 1,8-cineole, eugenol, camphor, carvone, citral, citronellol, limonene, kaur-16-ene and some 70 other identified compounds; which gives the drug its characteristic faint odour, more pronounced in the fresh flowers. The presence of phenolic acids (caffeic, *p*-coumaric and chlorogenic acids), scopoletin, tannins (approximately 2%, including the procyanidin dimers B-2 and B-4), leucoanthocyanidins, among others, has also been reported (*6*, *18*, *23*, *30*, *38–46*). The structures of the major constituents are presented below.

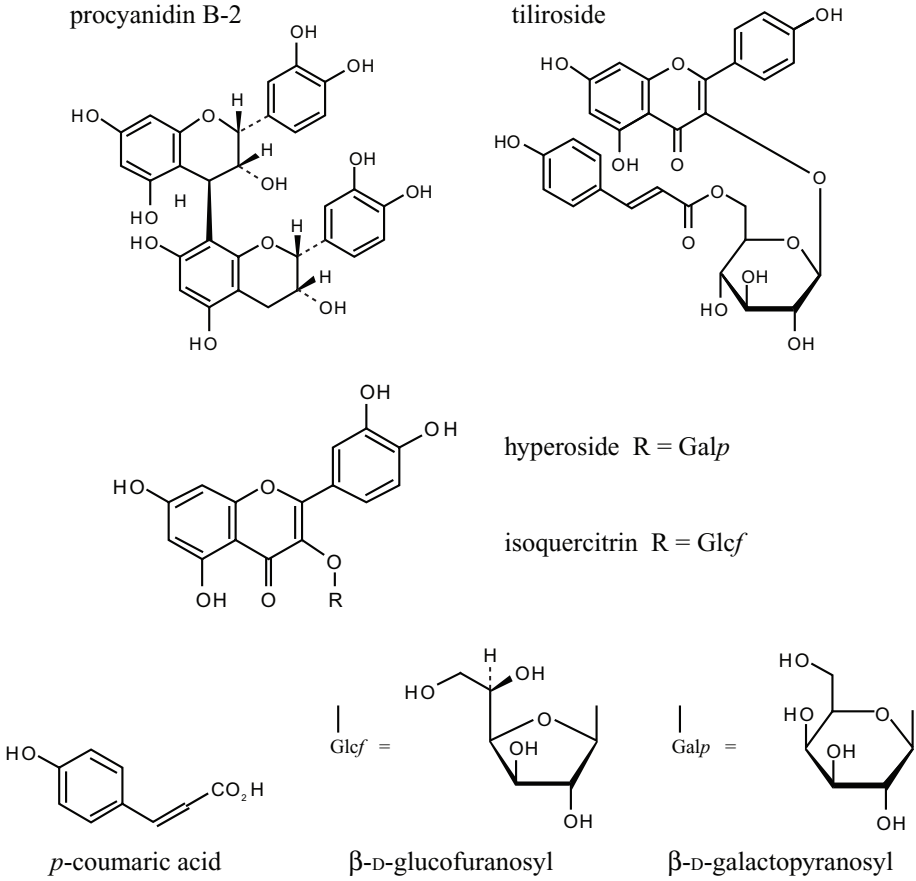
Medicinal uses

Uses supported by clinical data

No information was found.

Uses described in pharmacopoeias and well established documents

The Commission E approved the internal use of Flos Tiliae for colds and cold-related coughs (*45*). The use of the flowers as an antispasmodic and diaphoretic agent is indicated (*47*).



Uses described in traditional medicine

Flores Tiliae are used to treat insomnia (*48*, *49*). Traditionally, the flowers have been used for treatment of migraine, hysteria, arteriosclerotic hypertension, circulatory disorders and swelling of the ankle (*50–53*), cardiovascular and digestive complaints (*54*). Flos Tiliae are also used in urinary infections, influenza and anxiety (*20*, *22*, *55*).

Pharmacology

Experimental pharmacology

Action on lymphocyte proliferation

The aqueous extract of Flos Tiliae (1.5 g dried flowers in 20 ml of water) demonstrated stimulatory effects on lymphocyte proliferation in vitro. The test system consisted of suspensions of lymphoid cells, which were asepti-

cally removed from the lymph nodes of inbred mice; the final concentration of cells in culture was 2×10^6 cells/ml. The extract was tested at concentrations ranging from 0.5 to 80 µg/ml; control cells were treated with saline solution. The lymphocyte proliferation effect was mimicked by Ro 5-4864, a specific agonist of the peripheral benzodiazepine receptor and by Pk 11195, an agonist/antagonist of the same receptor; these agents were used as reference standards at a concentration of 5×10^{-7} M. Maximum stimulation of 170% was observed at a concentration of 20 µg/ml ($p < 0.05$). The synergistic effect of the extract with Ro 5-4864 suggests that the extract exerted its stimulatory action on cell proliferation by acting as a partial agonist on peripheral-type benzodiazepine binding sites (*56*).

Antitumour activity

The antiproliferative action of various extracts: aqueous (1.5 g flowers in 20 ml of water), dichloromethane (9 g flowers in 200 ml of dichloromethane) and ethanol (9 g flowers in 200 ml of ethanol) of *Tilia cordata* flowers on BW 5147 lymphoma cells and non-tumour lymphocytes was investigated. All extracts (at different concentrations) showed a selective action on tumour cells, inducing apoptosis. In the case of normal lymphocytes, these extracts suppressed mitogen-induced proliferation. The aqueous, dichloromethane and ethanol extracts inhibited proliferation of tumour and non-tumour cells in a concentration-dependent manner. From EC_{50} values, the dichloromethane extract proved to be the most active: it showed the greatest inhibition of cell proliferation, as shown by the EC_{50} values for both tumour cells (4.84 µg/ml) and non-tumour cells (14.12 µg/ml) ($p < 0.05$). Scopoletin, the main component in the dichloromethane extract had an antiproliferative action on BW 5147 cells, suggesting that it may be at least partly responsible for the activity displayed by this extract (*57*).

Antimicrobial activity

An aqueous extract of a commercial sample of Flos Tiliae demonstrated weak antibacterial activity in vitro against *Escherichia coli* and *Staphylococcus aureus* at a median inhibitory concentration (MIC) of 1 mg/ml/agar plate; *Staphylococcus aureus* strain Oxford at an MIC of 1.5 mg/ml; and against *Bacillus subtilis* at an MIC of 3.1 mg/ml (*58*).

A methanol extract of the dried flowers exhibited weak antifungal activity against *Aspergillus niger* in vitro at a concentration of 5 mg/ml/agar plate (*60*).

A 10% aqueous extract of dried Tiliae flowers demonstrated antiviral activity against influenza virus A2 (Manheim 57) in cell culture (*60*).

Smooth muscle effects

An aqueous extract of Tiliae flowers at a concentration of 0.08 g/ml produced a biphasic response in vitro, consisting of transient relaxation of rat duodenum followed by a constriction (*61*).

Toxicology

An infusion of Tiliae flowers (1:10) was assayed for anti-genotoxicity using the somatic mutation and recombinant test in *Drosophila melanogaster*. The infusion demonstrated desmutagenic activity (100% inhibition) against hydrogen peroxide used as an oxidative genotoxicant. These results could possibly be explained by synergism between phenolic components of the infusion and the hydrogen peroxide due to the known ability of phenols to scavenge reactive oxygen (*62*).

Clinical pharmacology

Diaphoretic action

The diaphoretic action of Tiliae flowers was investigated in an open controlled clinical trial in patients with uncomplicated catarrhal disease. Fifteen patients with catarrhal disease inhaled water vapour from a preparation made with two sachets of Tiliae flowers in 500 ml of water. Inhalation was maintained for 10 minutes at 40–50 °C. A control group of 15 patients inhaled vapour from coloured water. Fifteen minutes after inhalation all patients experienced a certain subjective relief with further improvement of their condition in the group that had inhaled the preparation of Tiliae flowers. In the control group improvement was observed only for the first 120 minutes, and after addition of other symptomatic treatment. In the authors' opinion the inhalation of a preparation of Tiliae flowers had an appreciable diaphoretic effect. As there was no statistical analysis of the data, an objective assessment of this investigation is not possible (*63*).

Adverse reactions

A case-report of occupational allergy in a 55-year-old woman has appeared in the scientific literature. The woman, a non-smoker, who was working as a cosmetician, had experienced recurrent itching and erythematous papulovesicular lesions on the backs of her hands for around 18 months, and had had a history of sneezing, nasal obstruction and watery eyes for some years when she came into contact with depilatory wax or flowers of *Tilia cordata*. Clinical examination, as well as routine laboratory parameters, remained normal. Total immunoglobulin E was 13 084 IU/ml and skin-prick tests showed positive reactions to common environmental allergens – grass and tree pollens, and to flowers. Specific immunoglobulin E antibodies for grass

and tree pollens were negative. The results of patch tests with *Tilia* flowers with a standard series and a series of plant allergens were positive. A bronchial challenge test was performed in an inhalation chamber for 30 minutes. In the first stage, the patient was challenged with placebo (potato flour); during the second stage (after 7 days), with depilatory wax that had been thermally activated, and after 14 days with dried flowers. Following such exposures, clinical symptoms of rhinoconjunctivitis appeared, and were observed for 48 hours after the challenges. In addition, increases in eosinophil and basophil proportions in nasal lavage and tear fluids were observed during the late phase of allergic reaction. A diagnosis of occupational allergy was made based on the positive results of the allergy tests, analysis of the clinical status and medical history, and the positive results of specific challenges (*64*).

Over a 5-year period, 1790 paediatric outpatients were observed for suspected allergic symptoms and 371 children were given a skin prick test to check for responses to aeroallergens. Aeroallergen sensitization due to *Tilia cordata* was observed in 11.4% of the paediatric patients examined (*65*).

Contraindications

If signs of hypersensitivity reaction appear (contact dermatitis or rhinoconjunctivitis), Flos Tiliae must not be used again.

Warnings

No information was found.

Precautions

General

No information was found.

Drug interactions

No information was found.

Drug and laboratory test interactions

No information was found.

Carcinogenesis, mutagenesis, impairment of fertility

No information was found.

Pregnancy: teratogenic effects

No information was found.

Pregnancy: non-teratogenic effects
No information was found.

Nursing mothers
No information was found.

Paediatric use
No information was found.

Dosage forms
Dried inflorescences with bracts are used for teas and other Galenical preparations for use in gargles, rinses and other topical applications, as well as for internal use (*36*).

Posology
(Unless otherwise indicated)
Daily dosage for internal use. Infusion: 2–4 g of dried flowers in 200 ml of boiling water, three times daily (*45*). Tincture: (1:5) in 45% ethanol, 1–2 ml, three times daily (*55*). Fluidextract: (1:1) in 25% ethanol, 24 ml, three times daily (*55*).
For gargles and rinses. Infusion: 4–5 tablespoonfuls of dried flowers in two 200-ml glasses (400 ml in total) of boiling water (*66*).
Dosage for external use. Bath: steep 4–5 tablespoonfuls of dried flowers in two 200-ml glasses (400 ml in total) of boiling water for 20 minutes and add to bath (*21*).

References
1. *USSR pharmacopoeia*, 11th ed. *Vol. 2*. Moscow, Meditsina, 1990.
2. *European Pharmacopoeia*, 5th ed. Strasbourg, European Directorate for the Quality of Medicines, 2005.
3. *British herbal pharmacopoeia.* Bournemouth, British Herbal Medicine Association, 1996.
4. Dragendorff G. *Die heilpflanzen der verschiedenen Völker und Zeiten. Ihre anwendung, wesentlichen bestandtheile und geschichte. Ein Handbuch für Arzte, Apotheker, Botaniker und Droguisten* [*The healing plants of various peoples and times. Their use, basic healing properties and history. A handbook for doctors, dispensing chemists, botanists and pharmacists*]. Stuttgart, Ferdinand Enke, 1898.
5. *Armenian national formulary for herbal medicines*. Yerevan, Drug and Medical Technology Agency, Ministry of Health of RA JSC, 2001.

6. Bisset NG, Wichtl M. *Herbal drugs and phytopharmaceuticals: A Handbook for practice on a scientific basis.* Stuttgart, Medpharm Scientific Publishers, 1994.
7. *Herb CD4: Herbal remedies.* CD-ROM. Stuttgart, Medpharm Scientific, 2001.
8. Petkov V, ed. *Sovremennaja fitoterapija*. Sofia, Meditsina i fizkultura, 1988.
9. *Technology transfer fact sheet*. Wisconsin, Center for Wood Anatomy Research, United States Department of Agriculture Forest Service (http://www2.fpl.fs.fed.us/TechSheets/HardwoodNA/pdf_files/tilaspeng.pdf).
10. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
11. Īriste V, Eniņa V. *Ārstniecības augu vārdnīca.* Riga, Medikamentu informācijas centers, 2000.
12. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
13. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.
14. Istudor V. *Farmacognozie, fitochimie, fitoterapie.* Bucharest. Editura Medicala, 1998.
15. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
16. Kuznetsova MA, Rybatshuk IZ. *Farmakognozija.* Moscow, Meditsina, 1984.
17. Yakovlev GP, Blinova KF, eds. *Lekarstvennoje rastitelnoje s'rjo. Farmakognozija.* St Petersburg, SpetzLit, 2004.
18. Muravjova DA, Sam'lina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
19. *Native trees of British Isles* (http://www.biodiversity.org.uk/ibs/envmath/resources/year3/env324/moffatt/HTMLfiles/t_cordata.htm).
20. Hammerman AF, Kadaev GN, Jacenko-Khmelevskii AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
21. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.
22. Chevallier A. *The encyclopaedia of medicinal plants*. London, Dorling Kindersley, 1996.
23. Yakovlev GP, Blinova KF, eds. *Rastenija dlja nas.* St Petersburg, Utchebnaja kniga, 1996.
24. Shishkin BK, Bobrov EG. *Flora SSSR. Vol. 15. Pod red.* Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1949.
25. Tamas M. *Botanica farmaceutica. Vol. III. Sistematica-Cormobionta.* Universitara Iuliu Hatieganu, Cluj Napoca, Editura Medicala, 1999.
26. Grinkevici NI, Ladiginoi EI, eds. *Pharmacognozia. Atlas*. *Pod red.* Moscow, Meditsina, 1989.
27. Gubanov IA, Krylova IL, Tihonova VL. *Dikorastushcie poleznye rastenia SSSR* [Wild useful plants of USSR]. Moscow, Mysl', 1976.

28. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR. 3-ie izd.* Kishinev, Shtiintsa, 1986.
29. Shishkin BK. *Botaniceskii atlas* [*Botanical Atlas*]/*pod red.* Moscow-Leningrad, Izdatel'stvo sel'skokhoziaistvennoi literatury, jurnalov i plakatov, 1963 [in Russian].
30. Muravjova DA. *Farmakognozija.* Moscow, Meditsina, 1991.
31. Toma C, Pugină R. *Anatomia plantelor medicinale – Atlas*. Bucharest, Editura Academiei României, 1998.
32. *Österreichisches Arzneibuch* [*Austrian Pharmacopoeia*]. Vienna, Verlag der Österreichischen Staatsdruckerei, 1990.
33. *Pharmacopoeia Helvetica,* 7th ed. Berne, Office Central Fédéral des Imprimés et du Matériel, 1987.
34. *Deutsches Arzneibuch* [*German Pharmacopoeia*], 10th ed. Supplement 1, 1992; Supplement 2, 1993. Stuttgart, Deutscher Apotheker Verlag.
35. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
36. *British herbal pharmacopoeia*. Vol. 1. Keighley, British Herbal Medicine Association, 1983.
37. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
38. Fleming T, ed. *Physicians' desk reference (PDR) for herbal medicines.* Montvale, Medical Economics Company, 2000.
39. *British herbal compendium*, Vol. 1. Bournemouth, British Herbal Medicine Association, 1992.
40. Bruneton J. *Pharmacognosy, phytochemistry. medicinal plants.* 2nd ed. Paris, Intercept, 1999.
41. Evans WC. *Trease and Evans' pharmacognosy*, 15th ed. Edinburgh, Saunders, 2000.
42. Heinrich M et al. *Fundamentals of pharmacognosy and phytotherapy.* Edinburgh, Churchill Livingstone, 2004.
43. Barnes J, Anderson LA, Philipson JD. *Herbal medicines: A guide for healthcare professionals,* 2nd ed. London, Pharmaceutical Press, 2002.
44. Toker G et al. The composition of essential oils from *Tilia* L. species growing in Turkey. *Journal of Essential Oil Research*, 1999, 11:369–374.
45. Blumenthal M et al, eds. *The Complete German Commission E monographs. Therapeutic guide to herbal medicines.* Austin, TX, American Botanical Council, 1998.
46. *Rastitel'nye resursy SSSR. Tsvetkovye rastenija, ih himitsheski sostav, ispolzovanije. Sem. Caprifoliaceae-Plantaginaceae*. *Vol. 2.* Leningrad, Nauka, 1987.
47. Sweetman SC ed. *Martindale. The complete drug reference*, 33rd ed. London, Pharmaceutical Press, 2002.
48. De Feo V et al. Traditional phytotherapy in the Peninsula Sorrentina, Campania, Southern Italy. *Journal of Ethnopharmacology*, 1992, 36:113–125.

49. Buchbauer G, Jirovetz L, Jaeger W. Passiflora and lime-blossoms: motility effects after inhalation of the essential oils and of some of the main constituents in animal experiment. *Archiv der Pharmazie*, 1992, 325:247–248.
50. Caceres A, Giron LM, Martinez AM. Diuretic activity of plants used for the treatment of urinary ailments in Guatemala. *Journal of Ethnopharmacology*, 1987, 19:233–245.
51. Bonet MA, Blanche C, Xirau JV. Ethnobotanical study in river Tenes valley (Catalonia, Iberian Peninsula). *Journal of Ethnopharmacology*, 1992, 37:205–212.
52. Al-Khalil S. A survey of plants used in Jordanian traditional medicine. *International Journal of Pharmacognosy*, 1995, 33:317–323.
53. Vazquez FM, Sauarez MA, Perez A. Medicinal plants used in the Barros area, Badajoz province (Spain). *Journal of Ethnopharmacology*, 1997, 44:81–85.
54. Bown D. *Encyclopaedia of herbs & their uses*. London, Royal Horticultural Society, 1996.
55. Newall CA et al., eds. *Herbal medicines: A guide for health-care professionals*. London, Pharmaceutical Press, 1996.
56. Anesini C, Werner S, Borda E. Effect of *Tilia cordata* flower on lymphocyte proliferation: participation of peripheral type benzodiazepine binding sites. *Fitoterapia*, 1999, 70:361–367.
57. Barreiro Arcos ML et al. *Tilia cordata* Mill. Extracts and scopoletin (isolated compound): differential cell growth effects on lymphocytes. *Phytotherapy Research*, 2006, 20:34–40.
58. Brantner A, Grein E. Antibacterial activity of plant extracts used externally in traditional medicine. *Journal of Ethnopharmacology*, 1994, 44:35–40.
59. Sardari S et al. Phytopharmaceuticals. Part 1. Antifungal activity of selected Iranian and Canadian plants. *Pharmaceutical Biology*, 1998, 36:180–188.
60. May G, Willuhn G. Antiviral activity of aqueous extracts from medicinal plants in tissue cultures. *Arzneimittel-Forschung*, 1978, 28:1–7.
61. Lanza JP, Steinmetz MD. Comparative actions of the aqueous extracts of seeds of *Tilia platyphylla* and *Tilia vulgaris* on the isolated intestine of the rat. *Fitoterapia*, 1986, 57:185–187.
62. Romero-Jiménes M et al. Genotoxicity and anti-genotoxicity of some traditional medicinal herbs. *Mutation Research*, 2005, 585:147–155.
63. Saller R et al. *Jahrestagung der Deutsche Gesellschaft für Phytotherapie* [*Annual convention of the German society for Phytotherapie*]. Münster, Deutsche Gesellschaft für Phytotherapie, 1988.
64. Krakowiak A et al. Occupational contact dermatitis with rhinoconjunctivitis due to *Tilia cordata* and colophonium exposure in a cosmetician. *Contact Dermatitis*, 2004, 51:34.
65. Loureiro G et al. Aeroallergens sensitization in an allergic paediatric population of Cova da Beira, Portugal. *Allergology and Immunopathology*, 2005, 33:192–198.
66. Ladynina EA, Morozova RS. *Fitoterapija*. Leningrad, Meditsina, 1987.

Radix Urticae*

Definition

Radix Urticae consists of the dried roots and rhizomes of *Urtica dioica* L., *U. urens* L. (Urticaceae), their hybrids or mixtures thereof (*1*, *2*).

Synonyms

Urtica dioica L.

Urtica gracilis Ait., *U. major* Kanitz., *U. urens maxima* Blackw. (*3*, *4*).

Urtica urens L.

Urtica minor Fuchs, *U. minor* Moench., *U. urens minima* Dod. (*3*, *4*).

Selected vernacular names

Urtica dioica L.

Brennesselwurzel, common nettle, csalángyökér, gazaneh, grande ortie, greater nettle, grosse Brennessel, Haarnesselwurzel, Hanfnesselwurzel, hhurrayq, Nesselwurzel, nettle root, ortica, ortie, ortiga, pokrzywa, qurrays, racine d'ortie, raiz de ortiga, stinging nettle, tsuknida, zwyczajna (*4–6*).

Urtica urens L.

Dwarf nettle, Eiternessel, kleine Brennessel, lesser nettle, ortica minore, ortica piccola, ortie brulante, petite ortie, sha'reláguz, small nettle (*4*, *6–9*).

Geographical distribution

Urtica dioica is indigenous to Africa and western Asia, but is now found in all temperate regions of the world in Africa, North and South America, Asia, Australia and Europe (*3*, *4*, *6*, *7*, *10*).

Owing to the difficulty in botanical differentiation between *Urtica dioica* and *U. urens* in the wild, they are often harvested together. Although both species have a similar distribution, *U. urens* has become less widely distributed due to the reduction of its habitat (*3*).

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

Description

Urtica dioica L.

A herbaceous perennial with erect, green to purplish square stems, 30–150 cm high, with creeping roots; whole plant covered with stinging hairs. Leaves opposite, cordate at the base, oblong or ovate, finely toothed; upper surface dark green and underside paler. Flowers incomplete, small, green, dioecious (plant has either male or female flowers in separate inflorescences) and occur as racemes in axils of upper leaves; male or barren flowers have a perianth of 4 segments and 4 stamens, which are bent inwards at bud stage; female or fertile flowers have similar perianth surrounding a single 1-seeded carpel, bearing 1 style with a brush-like stigma. Fruit an achene (*3*, *8*).

Urtica urens L.

A herbaceous annual resembling *Urtica dioica*, but is smaller (usually up to 30 cm high), has smaller leaves and flowers are in short, mostly unbranched clusters; male and female flowers appear together in the same raceme. Glabrous except for the stinging hairs (*8*, *11*).

Plant material of interest: dried roots and rhizomes

General appearance

Rhizome cylindrical and tapering, occasionally branched, up to about 6 mm thick at upper end; outer surface yellowish-brown; internodes with deep longitudinal furrows, numerous smooth, very thin and wiry roots arising from the nodes; in the outer part, inner surface creamy-white with a central hollow; fracture fibrous and tough.

Root greyish-brown, irregularly twisted, about 5 mm thick, distinct longitudinal furrows; hollow in cross-section, cut surface white; fracture fibrous and tough (*1*, *7*).

Organoleptic properties

Odourless; taste: faintly aromatic, characteristically bitter (*1*).

Microscopic characteristics

Rhizome: thin cork composed of brown, thin-walled cells, a few rows of tangentially elongated cortical parenchyma and a pericyclic region with fairly numerous fibres; fibres usually in small groups, sometimes single; individual fibres greatly elongated with very thick, lignified walls; some cells of pericycle and outer part of the secondary phloem contain fairly large cluster crystals of calcium oxalate. Cambial region distinct and continuous, with narrow radial groups of vascular tissues separated by wide

medullary rays; secondary phloem mainly parenchymatous, whereas secondary xylem dense and completely lignified; medullary rays in secondary xylem show alternating areas of lignified and unlignified cells; lignified cells have moderately thickened walls and numerous simple pits. Pith composed of rounded, unlignified parenchyma.

Root: very thin cork, narrow phelloderm and secondary phloem and xylem with alternating areas of lignified and unlignified parenchyma in the wide medullary rays, as in the rhizome; a strand of primary xylem in the centre with a few small vessels (*1*).

Powdered plant material

Fibrous and pale beige. Fragments of greatly elongated pericyclic fibres, occurring singly or in groups, with thick and lignified walls, xylem vessels with bordered pits, associated with thick-walled fibres with slit-shaped pits; lignified, moderately thick-walled and pitted parenchyma from the medullary rays of xylem; abundant thin-walled parenchymatous cells, some containing large cluster crystals or scattered crystals of calcium oxalate; fragments of brownish cork (*1*).

General identity tests

Macroscopic and microscopic examinations (*1*, *2*), and thin-layer chromatography for scopoletin and phytosterols (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign matter

Not more than 2% (*1*).

Total ash

Not more than 8% (*2*).

Acid-insoluble ash

Not more than 3.5% (*1*).

Water-soluble extractive

Not less than 15% (*1*).

Loss on drying
Not more than 12% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*), and pesticide residues (*14*).

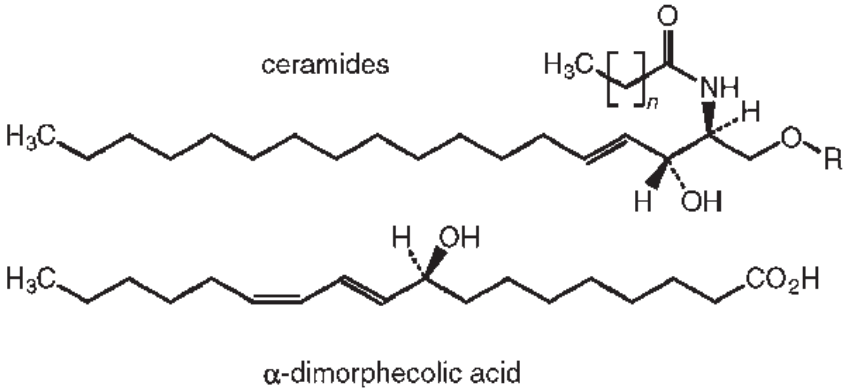
Heavy metals
For maximum limits and analysis for heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

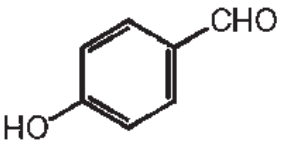
Other purity tests
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
In addition to thin-layer chromatography for qualitative analysis (*2*), enzyme-linked immunosorbent assay and high-performance liquid chromatography methods have also been developed to determine the concentration of *Urtica dioica* agglutinin in Radix Urticae (*15*, *16*). However, concentration limits need to be established.

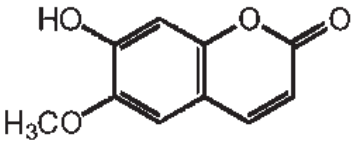
Major chemical constituents
A large number of compounds of different polarity and belonging to various chemical classes, including fatty acids, terpenes, phenylpropanes, lignans, coumarins, triterpenes, ceramides, sterols and lectins, have been isolated from Radix Urticae. Among these are oxalic acid, linoleic acid, 14-octacosanol, 13-hydroxy-9-*cis*,11-*trans*-octadecadienoic acid, α-dimorphecolic acid (9-hydroxy-10-*trans*,12-*cis*-octadecadienoic acid), scopoletin, *p*-hydroxybenzaldehyde, homovanillyl alcohol, β-sitosterol, stigmasterol, 24-*R*-ethyl-5α-cholestan-3β,6α-diol, campesterol, daucosterol (and related glycosides), secoisolariciresinol-9-O-β-D-glucoside, neoolivil, oleanolic acid, ursolic acid, *Urtica dioica* agglutinin and polysaccharides RP1-RP5 (*3–5*, *10*, *17–21*). The structures of the representative constituents are presented below.



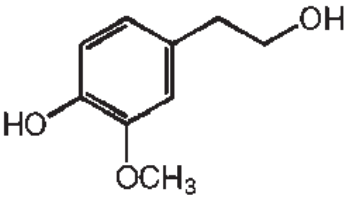
α-dimorphecolic acid



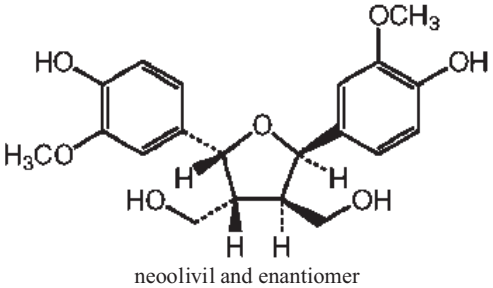
p-hydroxybenzaldehyde



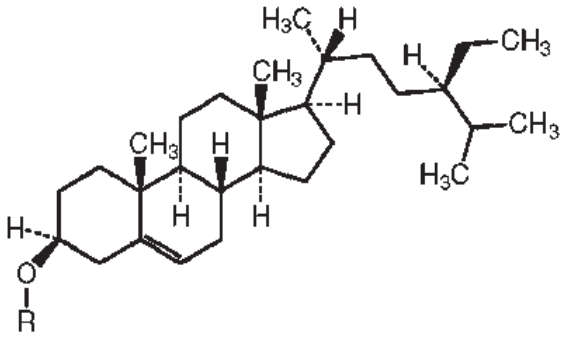
scopoletin



homovanillyl alcohol



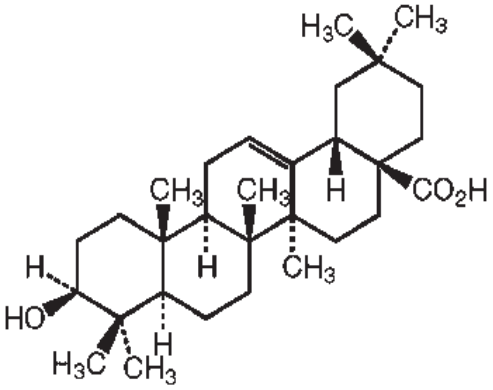
neoolivil and enantiomer



Glc = β-D-glucopyranosyl

β-sitosterol R = H

daucosterol R = Glc



oleanolic acid

Medicinal uses

Uses supported by clinical data

Symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, urinary retention) resulting from BPH stages I and II, as defined by Alken, in cases where diagnosis of prostate cancer is negative (*22–35*).

Uses described in pharmacopoeias and traditional systems of medicine

As a diuretic and for the treatment of rheumatism and sciatica (*6*).

Uses described in folk medicine, not supported by experimental or clinical data

Treatment of asthma, coughs, dandruff, diabetes, diarrhoea, eczema, fever, gout, haemorrhoids, nose bleeds, scurvy, snakebites and tuberculosis (*5*, *6*). The plant has also been used to stop uterine bleeding after childbirth, increase lactation and promote hair growth, and as a vermifuge (*5*, *6*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

An ethanol extract of Radix Urticae inhibited the activity of human leukocyte elastase and reduced the amount of the enzyme released by activated polymorphonuclear granulocytes during the inflammatory response. The extract also inhibited degradation of a peptide substrate in vitro by human leukocyte elastase (IC_{50} 3.6 µg/ml) and bovine elastin (IC_{50} 68 µg/ml) (*36*). Intragastric administration of a polysaccharide fraction isolated from Radix Urticae to rats (40 mg/kg body weight) suppressed carrageenan-induced footpad oedema for up to 20 h (*21*, *37*). The activity of the polysaccharides was comparable to that of indometacin (10 mg/kg body weight) (*21*, *37*).

Lymphocyte proliferation

A lyophilized aqueous extract (10 µg/ml) and a 40% alcohol extract of the roots (100 µg/ml) stimulated human lymphocyte proliferation in vitro by 63% and 100%, respectively (*21*, *37*). Polysaccharides isolated from an aqueous root extract induced human lymphocyte proliferation in vitro (10–100 µg/ml) (*21*, *37*). An ethyl acetate extract of the roots induced cell differentiation in human promyelocytic leukaemia HL-60 cells in vitro (ED_{50} 4 µg/ml) (*38*). *Urtica dioica* agglutinin (500 ng/ml), however, inhibited lymphocyte proliferation and the binding of epidermal growth factor to its receptor on A431 epidermoid cancer cells in vitro (*39*). The lectin also exhibited immunomodulatory effects on T-lymphocytes in a dose-dependent manner (*21*, *37*). *Urtica dioica* agglutinin bound to the cell membrane of prostatic hyperplastic cells (*40*) and inhibited their proliferation (*21*).

Effect on benign prostatic hyperplasia

Effect on sex hormone-binding globulin

Sex hormone-binding globulin (SHBG) is a blood plasma protein that binds to circulating androgens and estrogens, thereby regulating their free

concentration in plasma. The plasma membrane of the human prostate contains specific SHBG receptors, and SHBG appears to play a role in the development of BPH. A 10% hydroalcoholic extract of the root reduced the binding capacity of SHBG (isolated from human plasma) for 5α-dihydrotestosterone by 67% in vitro (*41*). An aqueous extract of the root (0.6–10.0 mg/ml) inhibited the binding of ^{125}I-labelled SHBG to human prostate membranes in vitro (*42*). The lignan, secoisolariciresinol, and a mixture of the isomeric compounds 13-hydroxy-9-*cis*,11-*trans*-octadecadienoic acid and 9-hydroxy-10-*trans*,12-*cis*-octadecadienoic acid isolated from a methanol root extract, reduced the binding of SHBG to 5α-dihydrotestosterone (*18*). Secoisolariciresinol and its main intestinal transformation products, (–)-3,4-divanillyltetrahydrofuran and enterofuran, displaced the binding of 5α-dihydrotestosterone to SHBG in vitro by 60%, 95% and 73%, respectively (*43*).

Enzymatic activity

Intragastric administration of a 30% ethanol extract of the root to male mice inhibited the activities of 5α-reductase and aromatase (ED_{50} 14.7 and 3.58 mg/ml, respectively) (*44*). However, a hydroalcoholic extract of the root dissolved in dimethyl sulfoxide did not inhibit the activity of 5α-reductase from human prostate cells in vitro (up to 500 µg/ml) (*45*). A standardized hydroalcoholic extract of the roots (IC_{50} 338 µg/ml) inhibited aromatase activity in vitro. A heptane-soluble fraction of the extract was the most effective inhibitor (IC_{50} 9 µg/ml) (*36*). Both ursolic acid and 14-octacosanol isolated from a methanol extract of the roots inhibited the activity of aromatase in vitro (*46*). 9-Hydroxy-10-*trans*,12-*cis*-octadecadienoic acid isolated from the roots inhibited the activity of aromatase in vitro (*19*). Butanol, ether, ethyl acetate and hexane extracts of the roots inhibited the activity of sodium- and potassium-adenosine triphosphatase isolated from prostatic hyperplastic cells by 27.6–81.5% (*47*). In addition, steroidal components of the roots, stigmast-4-en-3-one, stigmasterol and campesterol (1 µmol/l to 1 mmol/l), inhibited sodium- and potassium-adenosine triphosphatase activity by 23–67% (*47*).

Effect on prostate growth

Intragastric administration of a hexane extract of the roots (1.28 g daily) to castrated rats did not inhibit prostate growth stimulated by testosterone or dihydrotestosterone (*45*). Intraperitoneal administration of a hydroalcoholic extract of the roots (20 mg/kg body weight) suppressed testosterone-stimulated increases in prostate weight and prostatic ornithine decarboxylase activity in castrated rats (*48*). Daily oral administra-

tion of a hydroalcoholic extract of the root to dogs with BPH (30 mg/kg body weight) decreased prostate volume by 30% after 100 days of treatment (*49*).

The effect of various root extracts was assessed after implantation of the fetal urogenital sinus into the prostate gland of adult mice. Intragastric administration of a butanol, cyclohexane or ethyl acetate extract of the root (0.25 ml/daily for 3 weeks) had no effect on the development of BPH in mice. However, intragastric administration of the same dose of a 20% methanol extract of the root reduced the development of BPH by 51.4% (*50*).

Toxicology

The LD_{50} of an aqueous extract or infusion of the roots after intravenous administration to rats was 1721 mg/kg body weight and 1929 mg/kg body weight, respectively. Oral administration of an infusion of the roots to rats was well tolerated at doses up to 1310 mg/kg body weight (*3*).

Clinical pharmacology

Benign prostatic hyperplasia

Placebo-controlled clinical trials

Three double-blind, placebo-controlled clinical trials have assessed the efficacy of oral administration of Radix Urticae for the symptomatic treatment of lower urinary tract disorders resulting from BPH (*24*, *27*, *35*). One study assessed the efficacy of a 20% methanol extract of the roots in 50 men with BPH stages I and II (*35*). A significant increase in urine volume (by 43.7%; $P = 0.027$) and a significant decrease in serum levels of SHBG ($P = 0.0005$) was observed in patients treated with 600 mg extract daily for 9 weeks. A modest increase in maximum urinary flow of 8% was also observed in the treated group; however, it was not significant (*35*). Another study assessed the efficacy of a 20% methanol extract in 40 men with BPH. Treatment with 1200 mg extract daily for 6 weeks decreased the frequency of micturition and serum levels of SHBG (*27*). The third study assessed the efficacy of a methanol extract in the treatment of 32 men with BPH stage I (*24*). A 4–14% increase in average urinary flow and a 40–53% decrease in postvoid residual volume were observed in patients treated with 600 mg extract daily for 4–6 weeks (*24*).

Clinical trials without controls

Numerous clinical trials without controls have assessed the efficacy of oral administration of various Radix Urticae extracts (20% methanol or

30–45% ethanol) for the symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, dysuria, urine retention) resulting from BPH (*22*, *23*, *25*, *26*, *28–32*, *34*, *51*, *52*). One trial assessed the efficacy of a 40% ethanol extract of the roots in 67 men with BPH. Treatment with 5 ml daily for 6 months decreased nocturia and postvoid residual volume, but did not reduce prostate enlargement (*23*). In another trial, a 20% methanol extract of the roots was assessed in 89 men with BPH. Treatment with 600 mg daily decreased the postvoid residual volume in 75% of patients after 3–24 months (*25*). In a study of 26 men with BPH stage I or II, a decrease in prostate volume was observed in 54% of patients, and a decrease in postvoid residual volume was observed in 75% of patients, after treatment with 1200 mg methanol extract daily for 3–24 weeks (*26*). Ten men with BPH were treated with 30–150 drops of a 45% ethanol extract of the root daily for 30 days. After treatment, the postvoid residual volume decreased by 66% (*29*). In a study of 39 men with BPH stages I-III, an improvement in urinary flow, and a reduction in postvoid residual volume, nocturia and polyuria were seen in 95% of patients after 6 months of treatment with a 20% methanol extract (600–1200 mg daily) (*51*). Twenty-seven men with BPH stages I and II were treated with a 20% methanol extract of the roots for 3.5 months. Postvoid residual volume decreased significantly in 75% of patients ($P < 0.001$), and maximum urinary flow increased significantly in 50% of patients ($P < 0.002$) (*52*).

Three large-scale multicentre studies involving 14 033 men with BPH assessed the efficacy of a 20% methanol extract (*28*, *31*, *32*). In one study, a decrease in nocturia and polyuria was seen in 91% of patients after 6 months of treatment (*28*). In another study, a 50% decrease in nocturia was observed in patients treated with 1200 mg extract daily for 10 weeks (*31*). In the third study, significant improvements in both urinary flow and postvoid residual volume were observed in 4480 patients treated with 600–1200 mg extract daily for 20 weeks ($P < 0.01$) (*32*).

Effects on prostate morphology

Three studies without controls examined the effect of various methanol extracts of Radix Urticae on prostate morphology. Prostate cells were obtained from patients with BPH by needle biopsy, and were analysed for morphological changes before and after treatment. In two of the studies, cells were taken from the patients at various intervals during treatment (*53*, *54*). In the third study, cells were obtained once from the patients, and treatment with the extract was carried out in vitro (*55*). In the first study, 31 men with BPH stages I and II were treated orally with 1200 mg of a

20% methanol root extract daily for 20 weeks. Prostate cells were analysed every 4 weeks by fluorescent microscopy. After 4–16 weeks of treatment, an increase in nuclear volume, as well as hydropic swelling and vacuolization of the cytoplasm, were observed (*53*). In the second study, prostate cells from four men with BPH stage I were examined by electron microscopy. After 6 months of oral treatment with a 20% methanol extract (1200 mg daily), a reduction in the activity of smooth muscle cells and an increase in the secretory activity of glandular epithelial cells were observed (*54*). In the third study, prostate glandular epithelial cells from 33 patients with BPH were analysed by fluorescent microscopy following incubation of the cells in vitro with a 20% methanol extract of the root. Treatment with the extract caused an increase in nuclear volume, loosening of chromatin and hydropic swelling of the cytoplasm. In addition, the number of homogeneous secretory granules was reduced, indicating a reduction in the biological activity of these cells (*55*).

Contraindications

Radix Urticae is contraindicated in cases of known allergy to plants of the Urticaceae family. Owing to its effects on androgen and estrogen metabolism, the use of Radix Urticae during pregnancy and lactation and in children under the age of 12 years is contraindicated.

Warnings

Radix Urticae relieves the symptoms associated with BPH but does not have an effect on the size of the prostate. If symptoms worsen or do not improve, or in cases of blood in the urine or acute urinary retention, contact a physician.

Precautions

Pregnancy: teratogenic effects

See Contraindications.

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

Adverse reactions

Clinical studies have shown that extracts of Radix Urticae are well tolerated in humans. A few cases of minor transient gastrointestinal side-effects, such as diarrhoea, gastric pain and nausea (*32*, *35*), and allergic skin reactions (*32*), have been reported.

Dosage forms

Crude drug for infusion; hydroalcoholic extracts (*4*, *56*). Store in a well-closed container, protected from light and humidity (*2*, *13*).

Posology

(Unless otherwise indicated)

Daily dosage: 4–6 g crude drug or equivalent preparations as an infusion (*4*, *56*); 600–1200 mg dried 20% methanol extract (5:1) (*22*, *25*, *27*, *31*, *32*); 1.5–7.5 ml 45% ethanol extract (1:1) (*29*); 5 ml 40% ethanol extract (1:5) (*17*, *23*).

References

1. *British herbal pharmacopoeia*. London, British Herbal Medicine Association, 1996.
2. *Deutsches Arzneibuch*. Stuttgart, Deutscher Apotheker Verlag, 1998.
3. Bombardelli E, Morazzoni P. *Urtica dioica* L. *Fitoterapia*, 1997, 68:387–402.
4. Blaschek W et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Folgeband 2: Drogen A-K*, 5th ed. Berlin, Springer-Verlag, 1998.
5. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
6. Patten G. *Urtica. Australian Journal of Medical Herbalism*, 1993, 5:5–13.
7. Bisset NG. *Herbal drugs and phytopharmaceuticals.* Boca Raton, FL, CRC Press, 1994.
8. Grieve M. *A modern herbal. Vol. II*. New York, NY, Dover Publications, 1981.
9. Bedevian AK. *Illustrated polyglottic dictionary of plant names in Latin, Arabic, Armenian, English, French, German, Italian and Turkish languages.* Cairo, Argus & Papazian Press, 1936.

10. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier, 1995.
11. Tutin TG et al., eds. *Flora Europae. Vol. 4.* Cambridge, Cambridge University Press, 1976.
12. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
13. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
14. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
15. Willer F, Wagner H, Schecklies E. *Urtica* root extract. *Deutsche Apotheker Zeitung*, 1991, 131:1211–1217.
16. Samtleben R, Boos G, Wagner H. Novel enzyme-linked immunoassay for the quantitation of *Urtica dioica* agglutinin (UDA) in stinging nettle extracts and human excretions. *Phytomedicine*, 1996, 2(Suppl. 1):134.
17. *ESCOP monographs on the medicinal uses of plant drugs.* Fascicule 2. Elburg, European Scientific Cooperative on Phytotherapy, 1996.
18. Gansser D, Spiteller G. Plant constituents interfering with human sex hormone-binding globulin. Evaluation of a test method and its application to *Urtica dioica* root extracts. *Zeitschrift für Naturforschung*, 1995, 50c:98–104.
19. Kraus R, Spiteller G, Bartsch W. (10*E*,12*Z*)-9-Hydroxy-10,12-octadecadiensäure, ein Aromatase-Hemmstoff aus dem Wurzelextrakt von *Urtica dioica. Liebigs Annelen der Chemie*, 1990, 12:1205–1214.
20. Schilcher H, Effenberger S. Scopoletin und β-Sitosterol – zwei geeignete Leitsubstanzen für Urticae radix. *Deutsche Apotheker Zeitung*, 1986, 126:79–81.
21. Wagner H et al. Lektine und Polysaccharide – die Wirkprinzipien der *Urtica dioica* Wurzel. In: Boos G, ed. *Benigne Prostatahyperplasie*. Frankfurt, PMI, 1994.
22. Bauer HW et al. Endokrine Parameter während der Behandlung der benignen Prostatahyperplasie mit ERU. In: Bauer HW, ed. *Benigne Prostatahyperplasie II, klinische und experimentelle Urologie 19*. Munich, Zuckschwerdt, 1988.
23. Belaiche P, Lievoux O. Clinical studies on the palliative treatment of prostatic adenoma with extract of *Urtica* root. *Phytotherapy Research*, 1991, 5:267–269.
24. Dathe G, Schmid H. Phytotherapie der benignen Prostatahyperplasie (BPH). Doppelblindstudie mit Extraktum Radicis Urticae (ERU). *Urologie [B]*, 1987, 27:223–226.
25. Djulepa J. Zweijährige Erfahrung in der Therapie des Prosta-Syndroms. *Ärztliche Praxis*, 1982, 34:2199–2202.
26. Feiber H. Sonographische Verlaufsbeobachtungen zum Einfluss der medikamentösen Therapie der benignen Prostatahyperplasie (BPH). In: Bauer HW, ed. *Benigne Prostatahyperplasie II, klinische und experimentelle Urologie 19*. Munich, Zuckschwerdt, 1988.

27. Fisher M, Wilbert D. Wirkprüfung eines Phytopharmakons zur Behandlung der benignen Prostatahyperplasie (BPH). In: Rutishauser G, ed. *Benigne Prostatahyperplasie III, klinische und experimentelle Urologie 22*. Munich, Zuckschwerdt, 1992:79–83.
28. Friesen A. Statistische Analyse einer Multizenter-Langzeitstudie mit ERU. In: Bauer HW, ed. *Benigne Prostatahyperplasie II, klinische und experimentelle Urologie 19*. Munich, Zuckschwerdt, 1988:121–130.
29. Goetz P. Die Behandlung der benignen Prostatahyperplasie mit Brennesselwurzeln. *Zeitschrift für Phytotherapie*, 1989, 10:175–178.
30. Sonnenschein R. Untersuchung der Wirksamkeit eines prostatotropen Phytotherapeutikums (Urtica plus) bei benigner Prostatahyperplasie und Prostatitis – eine prospektive multizentrische Studie. *Urologie [B]*, 1987, 27:232–237.
31. Stahl HP. Die Therapie prostatischer Nykturie. *Zeitschrift für Allgemeine Medizin*, 1984, 60:128–132.
32. Tosch U et al. Medikamentöse Behandlung der benignen Prostatahyperplasie. *Euromed*, 1983, 6:1–3.
33. Vahlensieck W. Konservative Behandlung der benignen Prostatahyperplasie. *Therapiewoche Schweiz*, 1986, 2:619–624.
34. Vandierendounck EJ, Burkhardt P. Extractum radicis urticae bei Fibromyoadenom der Prostata mit nächtlicher Pollakisurie. *Therapiewoche Schweiz*, 1986, 2:892–895.
35. Vontobel HP et al. Ergebnisse einer Doppelblindstudie über die Wirksamkeit von ERU-Kapseln in der konservativen Behandlung der benignen Prostatahyperplasie. *Urologie [A]*, 1985, 24:49–51.
36. Koch E. Pharmacology and modes of action of extracts of Palmetto fruits (Sabal Fructus), stinging nettle roots (Urticae Radix) and pumpkin seed (Cucurbitae Peponis Semen) in the treatment of benign prostatic hyperplasia. In: Loew D, Rietbrock N, eds. *Phytopharmaka in Forschung und klinischer Anwendung.* Darmstadt, Verlag Dietrich Steinkopf, 1995:57–79.
37. Wagner H et al. Search for the antiprostatic principle of stinging nettle (*Urtica dioica*) roots. *Phytomedicine*, 1994, 1:213–224.
38. Suh N et al. Discovery of natural product chemopreventive agents utilizing HL-60 cell differentiation as a model. *Anticancer Research*, 1995, 15:233–239.
39. Wagner H et al. Studies on the binding of *Urtica dioica* agglutinin (UDA) and other lectins in an in vitro epidermal growth factor receptor test. *Phytomedicine*, 1995, 4:287–290.
40. Sinowatz F et al. Zur parakrinen Regulation des Prostatawachstums: Besteht eine Wechselwirkung zwischen dem basalen Fibroblasten-Wachstumsfaktor und dem Lektin UDA? In: Boos G, ed. *Benigne Prostatathyperplasie*. Frankfurt, PMI, 1994.
41. Schmidt K. The effect of an extract of Radix Urticae and various secondary extracts on the SHBG of blood plasma in benign prostatic hyperplasia. *Fortschritte der Medizin*, 1983, 101:713–716.

42. Hryb DJ et al. The effects of extracts of the roots of the stinging nettle (*Urtica dioica*) on the interaction of SHBG with its receptor on human prostatic membranes. *Planta Medica*, 1995, 61:31–32.
43. Schöttner M, Gansser D, Spiteller G. Lignans from the roots of *Urtica dioica* and their metabolites bind to human sex hormone-binding globulin (SHBG). *Planta Medica*, 1997, 63:529–532.
44. Hartmann RW, Mark M, Soldati F. Inhibition of 5α-reductase and aromatase by PHL-00801 (Prostatonin®), a combination of PY 102 (*Pygeum africanum*) and UR 102 (*Urtica dioica*) extracts. *Phytomedicine*, 1996, 3:121–128.
45. Rhodes L et al. Comparison of finasteride (Proscar®), a 5α-reductase inhibitor, and various commercial plant extracts in in vitro and in vivo 5α-reductase inhibition. *Prostate*, 1993, 22:43–51.
46. Gansser D, Spiteller G. Aromatase inhibitors from *Urtica dioica* roots. *Planta Medica*, 1995, 61:138–140.
47. Hirano T, Homma M, Oka K. Effects of stinging nettle root extracts and their steroidal components on the Na^+, K^+-ATPase of the benign prostatic hyperplasia. *Planta Medica*, 1994, 60:30–33.
48. Scapagnini U, Friesen A. *Urtica dioica*-Extrakt und Folgesubstanzen im Tierversuch. *Klinische und Experimentelle Urologie*, 1992, 22:138–144.
49. Daube G. Pilotstudie zur Behandlung der benignen Prostatahyperplasie bei Hunden mit Extractum Radicis Urticae (ERU). In: Bauer HW, ed. *Benigne Prostatahyperplasie II, klinische und experimentelle Urologie 19*. Munich, Zuckschwerdt, 1988:63–66.
50. Lichius JJ, Muth C. The inhibiting effects of *Urtica dioica* root extracts on experimentally induced prostatic hyperplasia in the mouse. *Planta Medica*, 1997, 63:307–310.
51. Maar K. Rückbildung der Symptomatik von Prostataadenomen. *Fortschritte der Medizin*, 1987, 105:50–52.
52. Romics I. Observations with Bazotona® in the management of prostatic hyperplasia. *International Urology and Nephrology*, 1987, 19:293–297.
53. Ziegler H. Cytomorphological study of benign prostatic hyperplasia under treatment with extract. Radicis Urticae (ERU) – preliminary results. *Fortschritte der Medizin*, 1982, 39:1823–1824.
54. Oberholzer M et al. Elektronenmikroskopische Ergebnisse bei medikamentös behandelter benigner Prostatahyperplasie. In: Bauer HW, ed. *Benigne Prostatahyperplasie*. Munich, Zuckschwerdt, 1986.
55. Ziegler H. Investigations of prostate cells under the effect of extract Radix Urticae (ERU) by fluorescent microscopy. *Fortschritte der Medizin*, 1983, 101:2112–2114.
56. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.

Styli cum stigmatis Zeae maydis

Definition

Styli cum stigmatis Zeae maydis consists of the whole or cut dried styles and stigmas of cultivated annual *Zea mays* L. (Poaceae/Gramineae) harvested during the ripening period (*1*).

Synonyms

Zea curagua Molina, *Z. indentata* Sturtev., *Z. indurata* Sturtev., *Z. japonica* Van Houtte, *Z. saccharata* Sturtev (*2*, *3*).

Selected vernacular names

Able, aburow, adakple, akple, artho, avari, avati, bada iringu, bajri, baomaimi, bap ngo, barajuar, bekalo, bhutta, blaifo, blarama, blikple, borona, buta, chhale, cholam, cholum, conac, corn, corn silk, cucuruz, durahkizan, durahshami, ekidid, fiso, froment des Indes, froment d'Inde, frumentone, garouilhe, garouillet, gaudumemekkah, goinjol, gorajonra, graine de turquet, grano siciliano, granoturco, gurulujonra, hausa, hintaherunu, hupfu, Indian corn, jagung, jaoari, jaori, jaorikhurdani, jawdra, jondra, jonra, jorna, junala, junri, kamh irrum, kandaja, kao põt, kao sãli, katsabotso, katsakandevolahy, katsamanga, katzaha, katzabazaha, keto, khalavan, khandaruz, khao koane, khao phot, khoshahemakki, khot, kitka, kon, kpkle, kpledzi, kukri, kukurudza, kukuruz, kukuruza, kukurūza, kukurydza, kuthi, lamari, le mais, lua ngo, ma khau li, maeo, Mais, maïs, maissi, maiz, maïz, maize, maize silk, maisgriffel, mahakaya, mahindi, maidis stigmata, mak, makai, maka, makaya, maki, makkajari, makkajowari, makkasholam, makkazonnalu, makkei, makki, mbemba, mbila, mealies, mekkejola, mel, melicatto, meliga, mielie, milho, millaral, millargou, misir, mokajanna, mukni, mungari, musukojola, nammanmo, ngo, okchokseoye, okmi, oksusoo, păpuşoi, paut, phoat, poone, popusoiu, porumb, potshatka, psheno turetskoeput, pyaungbu, sako, samputantastha, sana, shikhalu, sila, sila nivava lagi, simindi, stigmata maydis, stigmates de maïs, tomorokpshi, trigo de las indias, trigo de-turquia, tsako, tsakotsako, tuerkische korn, tuerkisher weizen, turkey corn, turkey wheat, upfu, watsikple, weizen türkischer, welschkorn, zaburro, zara del peru, zea, zurratulmakkah, zonallo, zondllo, yavanala, yumi, yumixu, yu shu shu (*4–19*).

Geographical distribution

Indigenous to Central America, it is now cultivated worldwide as green fodder or as a cereal crop (*2*, *5*, *20–23*).

Description

A robust monoecious annual plant, up to 3 m in height. Roots, fasciculate; often with prop roots from the lower nodes. Stems, erect, culm-internodes solid, smooth. Leaves, alternate, with sheathing base, ciliate ligule about 5 mm long, broadly linear or lanceolate blade, upper surface hairy, lower surface hairless, acuminate, parallel-veined, 25–100 cm long, 2–10 cm wide. Flowers, unisexual. Inflorescences, terminal panicle of male flowers, and spadix of female flowers. Male inflorescence (tassel) is a terminal large spreading panicle, about 30 cm long, formed by spike-like racemes of staminate spikelets. The spikelets are in pairs, one sessile, the other pedicelled, 8–12 mm long, awnless, 2-flowered, florets both male; glumes papery, equal, enclosing florets. Female inflorescence (spadeces or ears) variable in size and shape, borne on short branch with several short internodes with a papery sheath at each node, these form the husk and enclose the thick central axis (cob) on which the spikelets are arranged in 8–16(30) longitudinal rows; spikelets in pairs, 2-flowered, both sessile, awnless, the lower floret small, rarely female, the upper one female; glumes broad, rounded or notched at apex, fleshy towards base; styles projecting from apex of ear and look like tufts of hair, at first green, later red or yellow. Fruit, caryopsis with adherent pericarp; exposed between gaping lemma and palea at maturity; variable as to size, shape and colour (usually yellow but can be whitish or darker, almost black) (*2*, *5*, *24–27*).

Plant material of interest: dried styles and stigmas

General appearance

Slender, yellowish or brownish, filamentous styles, 5–20 cm long, exhibiting slender bifid stigmas 0.5–3.0 mm long. Viewed with a hand lens, they appear flattened and ribbon-like, or grooved and curled up, with spreading trichomes (*1*, *28*, *29*). In the cut form, the drug is made up of 5–10-mm long filamentous, channelled pieces of stigmata, pale yellowish or brownish red in colour (*5*). According to the *USSR pharmacopoeia*, the cut drug is composed of fragments of styles and stigmas having a length less than 7 mm, they are brownish, brownish red or light yellow in colour (*1*).

Organoleptic properties

Odour: slight, faint, characteristic; taste: insipid, slightly mucilaginous, somewhat sweetish (*1*, *5*, *28*, *29*).

Microscopic characteristics

Epidermal cells rectangular, often extended into multicellular trichomes 200–800 µm long, the basal portion consisting of 2–5 cells and the upper portion usually unicellular; multicellular and multiseriate trichomes, some of which are bluntly toothed; purplish red parenchymatous cells containing red colouring matter; two vascular bundles containing narrow tracheids with spiral or annular thickening (*1*, *5*, *28*, *29*).

Powdered plant material

Yellow powder with a slight odour and an insipid taste; rectangular epidermal cells often extending into multicellular trichomes; fragments of trichomes; parenchymatous cells with red contents (*28*).

General identity tests

Macroscopic and microscopic examinations (*1*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (*30*).

Chemical

No information available.

Foreign organic matter

Not more than 0.5% of organic matter (*1*). Brownish styles and stigmas or their fragments, not more than 3%. For cut drug: not more than 5% of fragments of drug having a length more than 7 mm and not more than 1% of fragments of drug having a length and diameter less than 0.2 mm (*1*).

Total ash

Not more than 8% (*29*) or not more than 7% (*1*).

Acid-insoluble ash

Not more than 2% of ash insoluble in concentrated hydrochloric acid (*29*) or not more than 2.5% of ash insoluble in 10% hydrochloric acid (*1*).

Sulfated ash

No information available.

Water-soluble extractive
Not less than 10% (*28*, *29*).

Alcohol-soluble extractive
Not less than 15% (*1*).

Loss on drying
Not more than 13% (*1*).

Pesticide residues
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*31*). For other pesticides, see the *European pharmacopoeia* (*31*) and the WHO guidelines on quality control methods for medicinal plant materials (*30*) and pesticide residues (*32*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (*30*).

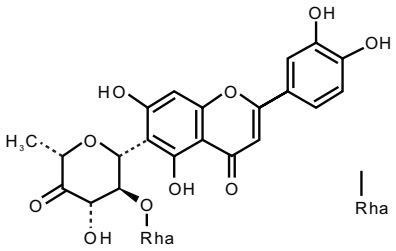
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (*30*) for the analysis of radioactive isotopes.

Other purity tests
Content of mineral matter, not more than 0.5% (*1*). Foreign matter, not more than 2% (*29*). Chemical and sulfated ash tests are to be established in accordance with national requirements.

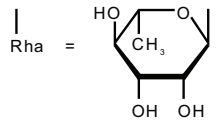
Chemical assays
The high-performance liquid chromatography method for the determination of maysin (*33*).

Major chemical constituents
The major constituents of the dried styles and stigmas are flavonoids especially 6-C-glycosylflavones; the major one is maysin. Among the flavonoids, a glycoside of luteolin, with small amounts of the corresponding 6-C-glycosyl analogues of apigenin and chrysoeriol; maysin-3´-methyl ether; rutin; anthocyanidins and flavan-4-ols (luteoforol, apiforol) are present. The flavone C-glycosides (chrysoeriol 6-C-β-fucopyranoside and chrysoeriol 6-C-β-boivinopyranosyl-7-O-β-glucopyranoside) have

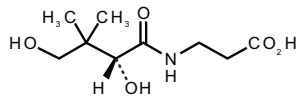
been isolated. There is also fixed oil (approximately 2%, including pantothenic and linoleic acids); essential oil (approximately 0.2%, containing carvacrol, α-terpineol, menthol and thymol); saponins (2–3%); tannin-like polyphenols (approximately 12%, probably chiefly proanthocyanidins); alkaloids (0.05%), steroids (stigmasterol and sitosterol); vitamin K_1, mucilage (relatively rich in potassium salts); minerals (notably approximately 2.7% of potassium); and carotenoids (*2*, *5*, *16*, *17*, *34–47*). The structures of the characteristic constituents are presented below.



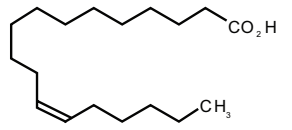
maysin



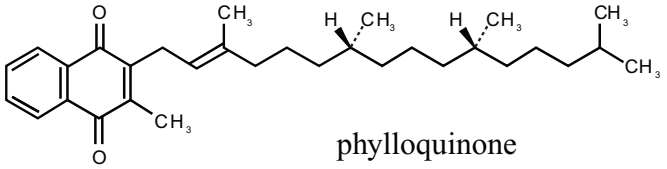
α-L-rhamnopyranosyl



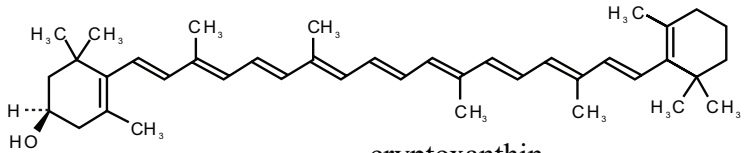
pantothenic acid



linoleic acid



phylloquinone



cryptoxanthin

Medicinal uses

Uses supported by clinical data

The stigmas and styles of *Zea mays* are used for the supportive treatment of chronic nephritis (*48*).

Uses described in pharmacopoeias and well established documents

The stigmas and styles of *Zea mays* are used for the treatment of cholangitis, hepatitis and cholecystitis (*43*), and of acute and chronic cystitis and urethritis (*36*). Also used in the treatment of heart disease (as a diuretic), hypertension, rheumatism and diabetes mellitus (*49*).

Uses described in traditional medicine

The stigmas and styles of *Zea mays* have been used externally in Mayan, Incan and American traditional medicine to treat bruises, swellings, sores, boils, erysipelas, dermatitis and external inflammations (*22*, *50*, *51*). Their internal uses in the treatment of gout, gastritis, bile congestion, alcoholism, prostatitis, benign prostatic hyperplasia, nocturnal enuresis and whooping cough have been described (*52*, *53*). They are also used as a sedative and laxative (*54–58*). Research in China and the former USSR countries indicates that the stigmas and styles of *Zea mays* lower blood pressure and reduce blood-clotting time (*21*, *59*). The stigmas and styles of *Zea mays* are also used in the treatment of cystitis and urethritis (*60*).

Pharmacology

Experimental pharmacology

Diuretic effect

Oral administration of a methanol extract of the styles and stigmas of *Zea mays* at a dose of 0.6 g/animal had diuretic effects in rats (*61*). A 50% ethanol-aqueous extract of fresh styles given by intragastric administration to rats at a dose of 40 ml/kg had diuretic action (*62*). When an infusion of dried stigmas of *Zea mays* was administered to rats at a concentration of 2 g/l (dry weight of stigmas) in drinking-water, a diuretic effect and decreased urinary magnesium and phosphate concentrations were observed. These effects were seen in animals fed a standard diet, but not in those receiving a high-protein or carbohydrate diet (*63*).

The effects of an aqueous extract of the styles and stigmas of *Zea mays* on the urinary excretion of water, sodium ions (Na^+), potassium ions (K^+) and uric acid were studied in water-loaded rats (2.5 ml/100 g bw) by continuous urine collection. Excretion of K^+ was observed in rats given an intragastric dose of 350 mg/kg (100.42–120.28 µEq/5 h/100 g bw), and of 500 mg/kg bw (94.97–134.32 µEq/5 h/100 g; $p < 0.01$). The higher dose resulted in diuresis as well (1.98–2.41 ml/5 h/100 g bw; $p < 0.05$). The effects of the 500 mg/kg bw dose of the extract on urine volume, Na^+, K^+, uric acid excretions, and glomerular function, were measured by creatinine and lithium ion (Li^+) clearance, in water-loaded rats (5 ml/100 g bw). Creatinine (294.6–241.7 µl/

min/100 g bw; $p < 0.05$) and the Na^+ filtered load (41.9–34.3, $p < 0.05$) decreased, and creatinine and Li clearances and Na^+ excretion were unchanged, while K^+ excretion (0.10–0.22 µEq/min/100 g bw; $p < 0.001$) increased. Thus, at a water-loading of 2.5 ml/100 g bw, the extract increased diuresis at a dose of 500 mg/kg, and increased excretion of K^+ at doses of 350 and 500 mg/kg. At a water-loading of 5 ml/100 g bw, excretion of K^+ increased at a dose of 500 mg/kg, but glomerular filtration decreased (*64*).

Prevention of diabetic complications

The aldehyde group of reducing sugar and amino residues in protein react and result in the formation of aggregates (advanced glycation end-products) such as N-ε-(carboxymethyl) lysine. Formation of these aggregates in the human body through glycation is associated with the induction of diabetic complications. Accumulation of N-ε-(carboxymethyl) lysine in the kidneys of subjects with diabetes has been reported. The inhibition of N-ε-(carboxymethyl) lysine accumulation by the flavone C-glucoside, chrysoeriol 6-C-β-fucopyranoside, isolated from the style of *Zea mays*, was calculated to be 80.7% (*46*). The same glycation inhibiting action was later shown for the corresponding 6-boivinoside. Similar derivatives of chrysoeriol, but with one more sugar attached, were inactive. Of the purines and pyrimidines present in *Zea mays*, only guanosine was found to be a glycation inhibitor (*65*).

The efficacy of a water extract of styles of *Zea mays* on diabetic nephropathy evoked by intravenous injection of streptozocin (40 mg/kg) was investigated in rats randomly allocated either to a control group (non-diabetic rats, $n = 5$), a non-treated group of diabetic rats ($n = 9$), or a group of treated diabetic rats ($n = 8$). The treated groups were given tap water containing an extract of dry styles at a concentration of 0.15% (w/v) (about 0.2 g/day), while the animals in the control and non-treated groups were given ordinary tap water. The rats were allowed free access to their water for 12 weeks. At 12 weeks, urine was collected for 24 hours using a metabolic cage, followed by the collection of a blood sample and a kidney sample after killing the animals. Plasma glucose, haemoglobin, fructosamine, creatinine, urinary creatinine, urinary albumin excretion and other clinical parameters were also measured. Creatinine clearance was calculated per 100 g of body weight. The difference in body weight observed between the non-treated diabetic rats and the control rats was significant ($p < 0.01$). The plasma glucose levels in the non-treated diabetic rats were significantly higher than in the control animals ($p < 0.01$); however, there was no difference in the plasma glucose, fructosamine or haemoglobin levels between treated diabetic rats and non-treated diabetic rats. The ratios of kidney weight to body weight were significantly higher in non-treated diabetic rats

than in the control rats ($p < 0.01$). Creatinine clearance in the treated diabetic rats was significantly lower than in the non-treated diabetic rats ($p < 0.05$). There was no significant difference in urinary albumin excretion between non-treated diabetic rats and treated diabetic rats. It was concluded that a water extract of the style of *Zea mays* prevented glomerular hyperfiltration and suppressed the progression of diabetic glomerular sclerosis in rats with streptozocin-induced diabetes (*66*).

Haematological effects

A methanol extract of dried styles expressed strong platelet aggregation-inhibiting activity with a median inhibitory concentration (IC_{50}) of 0.3 µg/ml by adenosine diphosphate (ADP), collagen, and arachidonic acid-induced platelet aggregation. The ethyl acetate extract of dried styles inhibited platelet aggregation induced by arachidonic acid (IC_{50} = 0.2 mg/ml), collagen (IC_{50} = 0.2 mg/ml), ADP (IC_{50} = 0.5 mg/ml), and platelet aggregating factor (IC_{50} = 0.7 mg/ml) (*67*, *68*). In cell culture, a chloroform extract of the dried stigmas of *Zea mays* inhibited the tumour necrosis factor-alpha (TNFα)-induced adhesion of endothelial cells to monocytic cells with a median effective dose (ED_{50}) of 70 µg/ml. Similar results were reported for bacterial lipopolysaccharide-induced cell adhesion with an ED_{50} of 82 µg/ml. The results obtained were significant at the $p < 0.01$ level. A 100% ethanol extract of the stigmas of *Zea mays* has also been reported to possess intercellular cell adhesion molecule-1-inhibitory activity against bacterial lipopolysaccharide-induced intercellular cell adhesion molecule-1-expression with an ED_{50} of 50 µg/ml. The same effect with an ED_{50} of 38 µg/ml was detected in an EAHY926 cell culture against TNFα-induced intercellular cell adhesion molecule-1-expression (*69*).

Haemodynamic effects

A hot aqueous extract of fresh stigmas produced a negative chronotropic and hypotensive effect in dogs anaesthetized with pentobarbital for up to 80 seconds by intravenous injection at a dose of 1.37–22 mg/kg (*70*). An aqueous-ethanol (1:1) extract of fresh styles (five parts of fresh plant material in 100 parts of water/ethanol) administered by gastric intubation to conscious rats at a dose of 40 ml/kg had a hypotensive effect (*71*).

Antibacterial, anticrustacean and anti-complementary activity

A 100% (non-diluted) ethanol extract of shade-dried stigmas of *Zea mays* (concentration 2.5 mg/disc) inhibited the growth of *Staphylococcus aureus* and *Candida albicans* in vitro, and exhibited an anticrustacean activity against *Artemia salina* (median lethal dose, 128 µg/ml) (*72*). A hot aque-

ous extract of dried stigmas of *Zea mays* (concentration 250 µg/ml) revealed an anti-complementary activity in a culture of cells from human serum (*73*).

Antioxidant activity

A methanol extract of the stigmas of *Zea mays* at various concentrations (0.2–4 mg/sample) inhibited lipid peroxide formation in liposomes, induced by the Fe^{2+}/ascorbate system, and measured spectrophotometrically by a thiobarbituric acid assay (*74*).

Antitumour activity

Intraperitoneal administration of an aqueous extract of dried stigmas and styles at a dose of 150 mg/kg on days 5, 6 and 7 after the start of the experiment revealed antitumour activity in the Ehrlich-carcinoma ascites model in mice (*75*).

Toxicology

A number of haematological factors in rats were altered by intragastric administration of an aqueous extract of the stigmas of *Zea mays* at doses of 50 and 100 mg/kg, but the effects at these dose levels were not considered significantly toxic (*76*). A 100% (non-diluted) ethanol extract of shade-dried stigmas of *Zea mays* (at a concentration of 70 µg/ml) expressed mutagenic activity in vitro on *Salmonella typhimurium* T1530 (*72*). The toxicity of a methanol-insoluble fraction of an aqueous extract of dried stigmas of *Zea mays* in rabbits was reported to be low. The effective intravenous dose for a diuretic action was documented as 1.5 mg/kg bw, and the LD_{50} as 250 mg/kg in rabbits (*78*). Stigmas of *Zea mays* contain an unidentified toxic principle described as being a cyanogenic compound (*78*). In the course of a study of the possible diuretic activity of a dried aqueous extract of the style and stigma of *Zea mays* (the main effect observed was an increased loss of sodium, potassium and chloride ions), the LD_{50} of the extract for male rats was 14.5 g/kg bw (*79*).

Clinical pharmacology

The diuretic effect of styles and stigmas of *Zea mays* has been tested in an open non-randomized clinical trial. Thirty patients with various cardiovascular diseases with accompanying fluid retention received an infusion of dried styles and stigmas (30 g in 200 ml of water), at a dose of one tablespoonful six times daily for 4–5 days. An increase in diuresis was observed in 65% of the patients. Observations in patients with other conditions have shown that the same dosage regime led to an increase in diuresis of about 36% in patients with chronic nephritis and of 32% in

patients with exudative pleuritis. Thus, the diuretic effect seems to be greatest in patients with cardiovascular diseases (*48*).

Adverse reactions

Allergic reactions including contact dermatitis and urticaria have been documented for the styles and stigmas of *Zea mays* (*36*).

Contraindications

Styli cum stigmatis Zeae maydis is contraindicated in patients with loss of appetite and a low body mass or, in view of the ability of this drug to decrease clotting time, those with high coagulability of blood (*76*, *80*). It is not recommended for irrigation therapy (hydro-colon therapy) in patients with oedema due to impaired heart or kidney function (*70*). If signs of hypersensitivity reactions appear (contact dermatitis and urticaria) the styles and/or stigmas of *Zea mays* must not be used again.

Warnings

No information was found.

Precautions

General

Prolonged use may result in hypokalaemia because of the diuretic action (*36*).

Drug interactions

No information was found.

Drug and laboratory test interactions

No information was found.

Carcinogenesis, mutagenesis, impairment of fertility

No information was found on carcinogenesis or impairment of fertility. A mutagenic effect has been reported for an ethanol extract (see Toxicology).

Pregnancy: teratogenic effects

No information was found.

Pregnancy: non-teratogenic effects

Styles and/or stigmas of *Zea mays* have been reported to stimulate uterine contractions in rabbits. Styles and/or stigmas should therefore not be taken during pregnancy without consultation with a physician (*36*).

Nursing mothers
No information was found.

Paediatric use
No information was found.

Dosage forms
Dried styles and/or stigmas used for infusion and other Galenical preparations for topical applications, as well as for internal use (*60*).

Posology
(Unless otherwise indicated)
For internal use. Daily dosage of dried styles and/or stigmas, 4–8 g or infusion (4–8 g in 200 ml of boiling water), one tablespoon three times daily (*36*). Tincture (1:5) in 25% ethanol, 5–15 ml three times daily (*60*). Liquid extract of stigmas (1:1) in 25% ethanol, 4–8 ml three times daily (*60*).
For external use: Cataplasm or bath, 4–5 tablespoons of stigmas in 400 ml (two glasses) of boiling water for 20 minutes applied to affected area or added to the bath water (*44*).

References
1. *USSR pharmacopoeia*. 11th ed. *Vol. 2*. Moscow, Meditsina, 1990.
2. *Herb CD4: Herbal Remedies,* CD-ROM. Stuttgart, Medpharm Scientific Publishers, 2001.
3. *Ecocrop host page*. Rome, Food and Agriculture Organization of the United Nations (http://ecocrop.fao.org/ecocrop/srv/en/home).
4. Kirtikar KR, Basu BD. *Indian medicinal plants.* In 4 vols. Delhi, M/S Bishen Singh Mahendra Pal Singh, 1918.
5. Bisset NG, Wichtl M. *Herbal drugs and phytopharmaceuticals: a handbook for practice on a scientific basis.* Stuttgart, Medpharm Scientific Publishers, 1994.
6. Schroeter AL, Panasiuk VA. *Dictionary of plant names.* Koeningstein, Koeltz Scientific Books, 1999.
7. Ivashin DS et al. *Lekarstvennyje rastenija Ukrainy.* Kiev, Urozhai, 1971.
8. Nosal MA, Nosal IM. *Lekarstvennyje rastenija i sposoby ih primenenija v narode.* Kiev, GMZ USSR, 1959.
9. Pakalns D. *Lexicon plantarum medicinalium polyglotum*. Riga, Tevans, 2002.
10. Īriste V, Eniņa V. *Ārstniecības augu vārdnīca.* Riga, Medikamentu informācijas centers, 2000.
11. Krall H et al. *Eesti taimede määraja*. Tartu, Eesti Loodusfoto, 1999.
12. Makaschvili A. *Lexicon botanicum. Nomina plantarum*. Tbilisi, Metsniereba, 1991.

13. Heyne K. *Tumbuhan berguna Indonesia.* Jilid I. Jakarta, Badan Litbang Kehutanan, 1987.
14. Burkill IH. *Economic products of the Malay peninsula. Vol. II.* London, Ministry of Agriculture (Malaysia), 1935.
15. Wren RC. *Potter's new cyclopedia of botanical drugs and preparations.* Saffron Walden, CW Daniel, 1988.
16. Kim IH et al. *Medicinal botany*. Seoul, Hakchang, 2003.
17. Ji OP et al. *Pharmacognosy*. Seoul, Dongmyung, 2003.
18. Grigorescu E, Ciulei I, Ursula S. *Index fitoterapeutic.* Bucharest, Editura Medicala, 1986.
19. Raal A, Odras K. *Väike ravimtaimede sõnastik: ladina, eesti, inglise, soome, vene*. Tartu, Celsius Healthcare, 2006.
20. Kuznetsova MA, Rybatshuk IZ. *Farmakognozija*. Moscow, Meditsina, 1984.
21. Hammerman AF, Kadaev GN, Jacenko-Khmelevskii AA. *Lekarstvennie rastenija*. Moscow, Visshaja shkola, 1983.
22. Chevallier A. *The encyclopedia of medicinal plants*. London, Dorling Kindersley, 1996.
23. Grieve M. *A modern herbal.* London, Tiger Books, 1998.
24. Warrier PK, Nambiar VPK, Ramankutty C, eds. *Indian Medicinal Plants.* V5. Chennai, Orient Longman, 1996.
25. Komarov VL, Rojevits BK, Shishkin BK, eds. *Flora SSSR. Vol. 2.* 26. Pod red. Moscow-Leningrad, Izdatel'stvo Akademii Nauk SSSR, 1934.
26. Geideman TS. *Opredeliteli vysshih pastenii Moldavskoi CCR*. 3-ie izd. Kishinev, Shtiintsa, 1986.
27. *Botaniceskii atlas.* Mosva, Izdatel'stvo selskohozeaistvennoi literatury, jurnalov i plakatov, 1963.
28. *British herbal pharmacopoeia*, *Vol. 1*. Bournemouth, British Herbal Medicine Association, 1990.
29. *British herbal pharmacopoeia*. Exeter, British Herbal Medicine Association, 1996.
30. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
31. *European pharmacopoeia*. Strasbourg, Council of Europe, 2005.
32. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (document WHO/FSF/FOS/97.7).
33. Snook ME, Widstrom NW, Gueldner RC. Reversed-phase high-performance liquid chromatographic procedure for the determination of maysin in corn silks. *Journal of Chromatography*, 1989, 477:439–447.
34. Barnes J, Anderson LA, Philipson JD. *Herbal medicines: A guide for healthcare professionals,* 2nd ed. London, Pharmaceutical Press, 2002.
35. Evans WC. *Trease and Evans pharmacognosy*, 15th ed. Edinburgh, Saunders, 2000.
36. Newall CA et al., eds. *Herbal medicines. A guide for health-care professionals*. London, Pharmaceutical Press, 1996.

37. Alijev PK, Prilipko LI. *Lekarstvennyje rastenija Azerbaidzhana*. Baku, Azerbaidzhanskoe gosudarstvennoe izdatelstvo, 1969.
38. Turova AD. *Lekarstvennyje rastenija SSSR I ih primenenija*. Moscow, Meditsina, 1974.
39. Smirnov MI, ed. *Vitaminy*. Moscow, Meditsina, 1974.
40. Muravjova DA, Samylina IA, Yakovlev GP. *Farmakognozija.* Moscow, Meditsina, 2002.
41. Muravjova DA. *Farmakognozija.* Moscow, Meditsina, 1991.
42. Matsku Y, Kreitsha I. *Atlas lekarstvennyh rasteniy.* Veda, Izd. Slovadskoi AN, 1981.
43. *Armenian national formulary for herbal medicines*. Yerevan, Drug and Medical Technology Agency Ministry of Health of RA JSC, 2001.
44. Sokolov SJ, Zamotaev IP. *Spravochnik po lekarstvennim rastenijam*. Moscow, Meditsina, 1988.
45. Suzuki R, Okada Y, Okuyama T. Two flavone C-glycosides from the style of Zea mays with glycation inhibitory activity. *Journal of Natural Products*, 2003, 66:564–565.
46. Suzuki R, Okada Y, Okuyama T. A new flavone C-glycoside from the style of Zea mays with glycation inhibitory activity. *Chemical and Pharmaceutical Bulletin,* 2003, 51:1186–1188.
47. Yakovlev GP, Blinova KF, ed. *Rastenija dlja nas.* St Petersburg, Utchebnaja kniga, 1996.
48. Temporary pharmacopoeial monograph. *Styli cum stigmatis Zeae maydis*. Tashkent, Institute of Plant Substances, Academy of Sciences, 2005.
49. *Medicinal plants in Viet Nam*. Manila, WHO Regional Publications, 1990 (Western Pacific Series, N.3).
50. Caceres A et al. Screening of antimicrobial activity of plants popularly used in Guatemala for the treatment of dermatomucosal diseases. *Journal of Ethnopharmacology*, 1987, 20:223–237.
51. Caceres A et al. Antigonorrhoeal activity of plants used in Guatemala for the treatment of sexually transmitted diseases. *Journal of Ethnopharmacology*, 1995, 48:85–88.
52. Han DS, Lee SJ, Lee HK. Ethnobotanical survey in Korea. In: Han BH et al. eds. *Proceedings of the Fifth Asian Symposium on Medicinal Plants and Spices*, Seoul, Korea, 1984, 5:125–144.
53. Martinez-Lirola MJ, Gonzalez-Tejero MR, Molero-Mesa J. Ethnobotanical resources in the province of Almeria, Spain: Campos de Nijar. *Economic Botany*, 1996, 50:40–56.
54. Boukef K, Souissi HR, Balansard G. Contribution to the study on plants used in traditional medicine in Tunisia. *Plantes Medicinales et Phytotherapie*, 1982, 16:260–279.
55. Darias V et al. Contribution to the ethnopharmacological study of the Canary Islands. *Journal of Ethnopharmacology*, 1986, 15:169–193.

56. Duke J, Martinez RV. *Amazonian ethnobotanical dictionary*. Boca Raton, FL, CRC Press, 1994.
57. De Feo V, Senatore F. Medicinal plants and phytotherapy in the Amalfitan coast, Salerno province, Campania, Southern Italy. *Journal of Ethnopharmacology*, 1993, 39:39–51.
58. Gurib-Fakim A et al. Medicinal plants of Rodrigues. *International Journal of Pharmacognosy*, 1996, 34:2–14.
59. Zadorozhnyi AM et al. *Spravotchnik po lekarstvennim rastenijam*. Moscow, Lesnaja promyshlennost', 1988.
60. *British herbal pharmacopoeia*. *Vol. 1.* Keighley, British Herbal Medicine Association, 1983.
61. Rebuelta M et al. Study of the diuretic effect of different preparations of the stigma of *Zea mays* L. *Planta Medica Phytotherapia*, 1987, 3:267–275.
62. De A Ribeiro R et al. Acute diuretic effects in conscious rats produced by some medicinal plants used in the state of Sao Paulo, Brazil. *Journal of Ethnopharmacology*, 1988, 24:19–29.
63. Grases F et al. The influence of *Zea mays* on urinary risk factors for kidney stones in rats. *Phytotherapy Research*, 1993, 7:146–149.
64. Velazquez DV et al. *Zea mays* L. extracts modify glomerular function and potassium urinary excretion in conscious rats. *Phytomedicine,* 2005, 12:363–369.
65. Suzuki R et al. Chemical constituents of the style of *Zea mays* L with glycation inhibitory activity. *Chemical and Pharmaceutical Bulletin,* 2007, 55:153–155.
66. Suzuki R, Okada Y, Okuyama T. The favorable effect of style of *Zea mays* L. on streptozotocin induced diabetic nephropathy. *Biological and Pharmaceutical Bulletin*, 2005, 28:919–920.
67. Okada Y et al. Search for naturally occurring substances for prevention against the complications of diabetes; inhibitory effect on aldose reductase and platelet aggregation. *Natural Medicine*, 1994, 48:324–329.
68. Okada Y et al. Search for naturally occurring substances for prevention against the complications of diabetes. Inhibitory effect on aldose reductase and platelet aggregation. *Proceedings of the International Symposium of Natural Medicine*, 1997, Kyoto, Japan, 1998:295–303.
69. Habtemariam S. Extract of corn silk (stigma of *Zea mays*) inhibits the tumour necrosis factor-alpha-and bacterial lipopolysaccharide-induced cell adhesion and ICAM-1 expression. *Planta Medica,* 1998, 64:314–318.
70. Martin N et al. Hemodynamic effects of a boiling water dialysate of maize silk in normotensive anaesthetized dogs. *Journal of Ethnopharmacology*, 1991, 31:259–262.
71. De A Ribeiro R et al. Acute antihypertensive effect in conscious rats produced by some medicinal plants used in the state of Sao Paulo. *Journal of Ethnopharmacology*, 1986, 15:261–269.
72. Alkofahi A et al. Biological activity of some Jordanian medicinal plant extracts. Part II. *Fitoterapia*, 1997, 68:163–168.

73. Shindo M et al. Studies on anti-complementary activity by Chinese herbs. *Proceedings of Symposium Wakan-Yaku*, 1983, 16: 6–80.
74. Maksimovic ZA, Kovacevic N. Preliminary assay on the antioxidative activity of maydis stigma extracts. *Fitoterapia*, 2003, 74:144–147.
75. Kosuge T et al. Studies on antitumor activities and antitumor principles of Chinese herbs. I. Antitumor activities of Chinese herbs. *Yakugaku Zasshi*, 1985, 105:791–795.
76. Garg DK, Goyal RN. Haematological and hepatotoxic effects of silken styles of corn in albino rats. *Journal of Applied Toxicology*, 1992, 12:359–363.
77. Hargono D. Information about the use of corn styles. *PhytoMedica*, 1990, 1:135–139.
78. Seigler DS. Plants of the northeastern United States that produce cyanogenic compounds. *Economic Botany*, 1976, 30:395–407.
79. Al-Ali M et al. *Tribulus terrestris*: preliminary study of its diuretic and contractile effects and comparison with *Zea mays*. *Journal of Ethnopharmacology*, 2003, 85:257–260.
80. Ladynina EA, Morozova RS. *Fitoterapija*. Leningrad, Meditsina, 1987.

Annex

Participants in the WHO Consultation on Medicinal Plants Commonly Used in NIS, WHO Headquarters, Geneva, 5–7 July, 2006

Dr Zamirbek Akaev, Head of Drug Information Center, Department of Drug Provision and Medical Equipment, Bishkek, Kyrgyzstan

Dr Elene Amirejibi, Head of the Department of Traditional Medicine, Ministry of Labour, Health and Social Affairs of Georgia, Tbilisi, Georgia

Professor Elmira Amroyan, Head, Pharmacological Commission, Scientific Centre of Drug and Medical Technology Expertise, Yerevan, Armenia

Dr Robert Ancuceanu, Head of Service in the National Medicines Agency, Bucharest, Romania

Dr Shaknoza Azimova, Director of Institute of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, Uzbekistan

Dr Kemal Hüsnü Can Başer, Professor of Pharmacognosy, Faculty of Pharmacy, Anadolu University, Eskisehir, Turkey

Mrs Annagozel Bayrambabayeva, Lead Specialist of Statistics and Information Department of Ministry of Health and Medical Industry of Turkmenistan, Ashgabat, Turkmenistan

Dr Gulchekhra Boltabaeva, Scientific Secretary, Pharmacopoeia Committee, Ministry of Health of Uzbekistan, Tashkent, Uzbekistan

Professor Raymond Boudet-Dalbin, Faculty of Pharmacy, University of Paris, Paris, France

Dr Elene Chikobava, Chief Specialist of Pharmacopeia Department, Drug Agency, Ministry of Labour, Health and Social Affairs of Georgia, Tbilisi, Georgia

Dr Maria Cojocaru-Toma, Chief, Department of Pharmaceutical Inspection, National Drug Agency, Chisinau, Moldova

Professor Vincenzo De Feo, Department of Pharmaceutical Sciences, State University of Salerno, Fisciano (Salerno), Italy

Mr Tzvetomir Mario Deliyski, Expert, Council on Phytogalenic and Homeopathic Medicinal Products, Bulgarian Drug Agency, Sofia, Bulgaria
Professor Francesco De Simone, Dean, Faculty of Pharmacy, State University of Salerno, Fisciano (Salerno), Italy
Professor Norman Farnsworth, Director of WHO Collaborating Centre for Traditional Medicine, College of Pharmacy, University of Illinois at Chicago, Chicago, USA
Professor Hassan Farsam, Department of Medical Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
Dr Tatyana Garnik, Head, Committee on Traditional and Alternative Medicine, Ministry of Health, Kiev, Ukraine
Ms Lilit Ghazaryan, Deputy Director, Scientific Centre of Drug and Medical Technology Expertise, Yerevan, Armenia
Dr Benjamin Gilbert, FarManguinhos – FIOCRUZ, Rio de Janeiro, Brazil
Dr Angela Gisca, Chisinau, Moldova
Dr Natalia Gurina, Head, Department of Pharmacognosy and Botany, Vitebsk State Medical University, Vitebsk, Belarus
Dr Saule Ismailova, Head of the Division, Pharmacy Committee, Ministry of Health of Kazakhstan, Astana, Kazakhstan
Professor Yusif Karimov, Head of Herbal Medicine's Faculty, Azerbaijan Medical University, Baku, Azerbaijan
Dr Konstantin Keller, Department for International Pharmaceutical Affairs, Federal Ministry of Health and Social Security, Bonn, Germany
Dr Artyk Kokanov, Director of Medical Drugs Institutes, Ashgabat, Turkmenistan
Ms Nedjibe Mametova, Expert, Pharmacopoeia Committee, Department of Drug Provision and Medical Equipment, Bishkek, Kyrgyzstan
Ms Yevgenia Melkonyan, Expert on Traditional/Alternative Medicine, Scientific Centre of Drug and Medical Technology Expertise, Yerevan, Armenia
Mr Mirzo Nazarov, Head of the Pharmacognosy and OEP Department of Tajik State Medical University; Director of Scientific – Experimental Pharmaceutical Centre under the Ministry of Health of Republic of Tajikistan, Dushanbe, Tajikistan
Dr Maria Niculescu, Head of Service in the National Medicines Agency, Bucharest, Romania
Mrs Princess Thomas Osbourne, Director, Standards & Regulation Division, Ministry of Health, Kingston, Jamaica
Professor Tamàs Paàl, Director-General, National Institute of Pharmacy, Budapest, Hungary

Dr Ain Raal, Assistant-Professor, Head of the Chair of Pharmacognosy and Pharmaceutical Management, Institute of Pharmacy, University of Tartu, Tartu, Estonia

Dr Liudmila Reutskaya, Head, Department of Pharmaceutical Inspection and Organization of Pharmaceuticals Provision, Ministry of Health, Minsk, Belarus

Mr Zafar Sangov, General Director of Joint Enterprise "Tajik Adjanta Pharma Limited", Dushanbe, Tajikistan

Dr Larisa Soloviova, Researcher, Laboratory of Control and Certification of Medicines, National Drug Agency, Chisinau, Moldova

Dr Victor Tumanov, Rector, Medical Institute of the Ukrainian Association of Folk Medicine, Pharmaceutical Center, Ministry of Health of Ukraine, Kiev, Ukraine

Mr Engin Ural, Secretary General, Environment Foundation of Turkey, Ankara, Turkey

Dr Mehtap Varel, Pharmacist, General Directorate of Pharmaceuticals, Ministry of Health, Ankara, Turkey

Dr Annet Zakaryan, Consultant in the Herbal Products, AZNAR Consulting, Ann Arbor, MI, USA

WHO Secretariat

Dr Samvel Azatyan, Technical Officer, Traditional Medicine (TRM), Department of Technical Cooperation for Essential Drugs and Traditional Medicine (TCM)

Dr Yingrong Du, Technical Officer, Traditional Medicine (TRM), Department of Technical Cooperation for Essential Drugs and Traditional Medicine (TCM)

Ms Yukiko Maruyama, Scientist, Traditional Medicine (TRM), Department of Technical Cooperation for Essential Drugs and Traditional Medicine (TCM)

Dr Xiaorui Zhang, Coordinator, Traditional Medicine (TRM), Department of Technical Cooperation for Essential Drugs and Traditional Medicine (TCM)

Selected WHO publications of related interest

Information on medicinal plants:

WHO monographs on selected medicinal plants, Volume 4
(ISBN 978 92 4 154705 5), 2009

WHO monographs on selected medicinal plants, Volume 3
(ISBN 978 92 4 154702 4), 2007

WHO monographs on selected medicinal plants, Volume 2
(ISBN 92 4 154537 2), 2002

WHO monographs on selected medicinal plants, Volume 1
(ISBN 92 4 154517 8), 1999

Quality assurance and control of herbal medicines:

WHO Guidelines on good agricultural and collection practices (GACP) for medicinal plants
(ISBN 92 4 154627 1), 2003

WHO good agricultural and collection practices (GACP) monograph on Artemisia annua L.
(ISBN 978 92 4 159443 1), 2006

Quality control methods for medicinal plant materials
(ISBN 92 4 154510 0), 1998

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms
(ISBN 92 4 154513 5), 1998

WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues
(ISBN 978 92 4 159444 8), 2007

WHO guidelines for good manufacturing practices (GMP) for herbal medicines
(ISBN 978 92 4 154716 1), 2007

Regulation, evaluation and safety monitoring of herbal medicines:

Summary report of the global survey on national policy on traditional medicine and complementary/alternative medicine and regulation of herbal medicines
(ISBN 92 4 159323 7), 2005

WHO guidelines on safety monitoring and pharmacovigilance of herbal medicines
(ISBN 92 4 159221 4), 2004

General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine
(WHO/EDM/TRM/2000.1), 2000

Consumer information:

WHO guidelines on development of consumer information on proper use of traditional medicine and complementary/alternative medicine
(ISBN 92 4 159170 6), 2004

Further information on WHO technical documents in the field of traditional medicine including those listed above, can be found at the address below:
http://apps.who.int/medicinedocs/en/cl/CL10/

Despite the increasing use of herbal medicines, there is still a significant lack of research data in this field, so that the WHO monographs are playing an increasingly important role.

In order to meet demands of the Newly Independent States (NIS) to regulate herbal medicines and to ensure safety, efficacy and quality of herbal medicines, WHO has provided technical guidance and worked with the national health authorities of interested NIS and Countries of Central and Eastern Europe (CCEE) to develop monographs on commonly-used medicinal plants in the NIS.

The NIS monographs include comprehensive scientific information on the safety, efficacy and quality of medicinal plants. The format of the NIS monographs is the same as of the WHO monographs on medicinal plants. Each monograph follows a standard format, with information presented in two parts, followed by a reference list. The first part presents pharmacopoeial summaries for quality assurance, while the second part includes sections on medicinal uses, pharmacology, safety issues and dosage forms.

The monographs may serve as an authoritative source of information for national drug regulatory authorities, since they have been fully involved in the development of the monographs. However, it should also be emphasized that the descriptions included in the section on medicinal uses should not be taken as implying WHO's official endorsement or approval and also not intended to replace any national monographs or national pharmacopoeia of medicinal plants. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of information exchange.

ISBN 978 92 4 159772 2