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WHO also acknowledges with thanks the members of the advisory group that met in Beijing, China, in 1994, to draw up a list of medicinal plants for which monographs should be prepared, the more than 100 experts who provided comments and advice on the draft texts, and those who participated in the WHO Consultation held in Munich, Germany, in 1996 to review the monographs (see Annex). Finally, WHO would like to thank the Food and Agriculture Organization of the United Nations and the United Nations Industrial Development Organization for their contributions and all those who submitted comments through the World Self-Medication Industry, a nongovernmental organization in official relations with WHO.

Introduction

During the past decade, traditional systems of medicine have become a topic of global importance. Current estimates suggest that, in many developing countries, a large proportion of the population relies heavily on traditional practitioners and medicinal plants to meet primary health care needs. Although modern medicine may be available in these countries, herbal medicines (phytomedicines) have often maintained popularity for historical and cultural reasons. Concurrently, many people in developed countries have begun to turn to alternative or complementary therapies, including medicinal herbs.

Few plant species that provide medicinal herbs have been scientifically evaluated for their possible medical application. Safety and efficacy data are available for even fewer plants, their extracts and active ingredients, and the preparations containing them. Furthermore, in most countries the herbal medicines market is poorly regulated, and herbal products are often neither registered nor controlled. Assurance of the safety, quality, and efficacy of medicinal plants and herbal products has now become a key issue in industrialized and in developing countries. Both the general consumer and health-care professionals need up-to-date, authoritative information on the safety and efficacy of medicinal plants.

During the fourth International Conference of Drug Regulatory Authorities (ICDRA) held in Tokyo in 1986, WHO was requested to compile a list of medicinal plants and to establish international specifications for the most widely used medicinal plants and simple preparations. Guidelines for the assessment of herbal medicines were subsequently prepared by WHO and adopted by the sixth ICDRA in Ottawa, Canada, in 1991.[1] As a result of ICDRA's recommendations and in response to requests from WHO's Member States for assistance in providing safe and effective herbal medicines for use in national health-care systems, WHO is now publishing this first volume of 28 monographs on selected medicinal plants; a second volume is in preparation.

Preparation of the monographs

The medicinal plants featured in this volume were selected by an advisory group in Beijing in 1994. The plants selected are widely used and important in

[1] Guidelines for the assessment of herbal medicines. In: *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Volume 1*. Geneva, World Health Organization, 1997:31–37.

all WHO regions, and for each sufficient scientific information seemed available to substantiate safety and efficacy. The monographs were drafted by the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, United States of America. The content was obtained by a systematic review of scientific literature from 1975 until the end of 1995: review articles; bibliographies in review articles; many pharmacopoeias—the International, African, British, Chinese, Dutch, European, French, German, Hungarian, Indian, and Japanese; as well as many other reference books.

Draft monographs were widely distributed, and some 100 experts in more than 40 countries commented on them. Experts included members of WHO's Expert Advisory Panels on Traditional Medicine, on the International Pharmacopoeia and Pharmaceutical Preparations, and on Drug Evaluation and National Drug Policies; and the drug regulatory authorities of 16 countries.

A WHO Consultation on Selected Medicinal Plants was held in Munich, Germany, in 1996. Sixteen experts and drug regulatory authorities from Member States participated. Following extensive discussion, 28 of 31 draft monographs were approved. The monograph on one medicinal plant was rejected because of the plant's potential toxicity. Two others will be reconsidered when more definitive data are available. At the subsequent eighth ICDRA in Bahrain later in 1996, the 28 model monographs were further reviewed and endorsed, and Member States requested WHO to prepare additional model monographs.

Purpose and content of the monographs

The purpose of the monographs 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 Member States;
- provide models to assist Member States in developing their own monographs or formularies for these or other herbal medicines; and
- facilitate information exchange among Member States.

Readers will include members of regulatory authorities, practitioners of orthodox and of traditional medicine, pharmacists, other health professionals, manufacturers of herbal products, and research scientists.

Each monograph contains two parts. The first part consists of pharmacopoeial summaries for quality assurance: botanical features, distribution, identity tests, purity requirements, chemical assays, and active or major chemical constituents. The second part summarizes clinical applications, pharmacology, contraindications, warnings, precautions, potential adverse reactions, and posology.

In each pharmacopoeial summary, the *Definition* section provides the Latin binomial pharmacopoeial name, the most important criterion in quality assurance. Latin pharmacopoeial synonyms and vernacular names, listed in the

sections *Synonyms* and *Selected vernacular names*, are those names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International Rules of Nomenclature.

For example, *Aloe barbadensis* Mill. is actually *Aloe vera* (L.) Burm. *Cassia acutifolia* Delile and *Cassia angustifolia* Vahl., often treated in separate monographs, are now believed to be the same species, *Cassia senna* L. *Matricaria chamomilla* L., *M. recutita* L., and *M. suaveolens* L. have been used for many years as the botanical name for camomile. However, it is now agreed that the name *Chamomilla recutita* (L.) Rauschert is the legitimate name.

The vernacular names listed are a selection of names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. The lists are not complete, but reflect the names appearing in the official monographs and reference books consulted during preparation of the WHO monographs and 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).

A detailed botanical description (under *Description*) is intended for quality assurance at the stages of production and collection, whereas the detailed description of the drug material (under *Plant material of interest*) is for the same purpose at the manufacturing and commerce stages. *Geographical distribution* is not normally found in official compendia, but it is included here to provide additional quality assurance information.

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 Member State authorities.

Each medicinal plant and the specific plant part used (the drug) 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 section *Major chemical constituents*.

The second part of each monograph begins with a list of *Dosage forms* and of *Medicinal uses* categorized as those uses supported by clinical data, those uses described in pharmacopoeias and in traditional systems of medicine, and those uses described in folk medicine, not yet supported by experimental or clinical data.

The first category includes medical indications that are well established in some countries and that have been validated by clinical studies documented in the world's scientific literature. The clinical trials may have been controlled, randomized, double-blind studies, open trials, or well-documented observations of therapeutic applications. Experts at the Munich Consultation agreed to include Folium and Fructus Sennae, Aloe, Rhizoma Rhei, and Herba Ephedrae

in this category because they are widely used and their efficacy is well documented in the standard medical literature.

The second category includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or national monographs. Well-established uses having a plausible pharmacological basis and supported by older studies that clearly need to be repeated are also included. The references cited provide additional information useful in evaluating specific herbal preparations. The uses described should be reviewed by local experts and health workers for their applicability in the local situation.

The third category refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. The appropriateness of these uses could not be assessed, owing to a lack of scientific data to support the claims. The possible use of these remedies must be carefully considered in the light of therapeutic alternatives.

The final sections of each monograph cover *Pharmacology* (both experimental and clinical); *Contraindications* such as sensitivity or allergy; *Warnings*; *Precautions*, including discussion of drug interactions, carcinogenicity, teratogenicity and special groups such as children and nursing mothers; *Adverse reactions*; and *Posology*.

Use of the monographs

WHO encourages countries to provide safe and effective traditional remedies and practices in public and private health services.

This publication is not intended to replace official compendia such as pharmacopoeias, formularies, or legislative documents. The monographs are intended primarily to promote harmonization in the use of herbal medicines with respect to levels of safety, efficacy, and quality control. These aspects of herbal medicines depend greatly on how the individual dosage form is prepared. For this reason, local regulatory authorities, experts, and health workers, as well as the scientific literature, should be consulted to determine whether a specific herbal preparation is appropriate for use in primary health care.

The monographs will be supplemented and updated periodically as new information appears in the literature, and additional monographs will be prepared. WHO would be pleased to receive comments and suggestions, to this end, from readers of the monographs.

Finally, I should like to express our appreciation of the support provided for the development of the monographs by Dr H. Nakajima and Dr F. S. Antezana during their time as Director-General and Assistant Director-General, respectively, of WHO.

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Bulbus Allii Cepae

Definition

Bulbus Allii Cepae is the fresh or dried bulbs of *Allium cepa* L. (Liliaceae) or its varieties and cultivars.

Synonyms

Allium esculentum Salisb., *Allium porrum cepa* Rehb. (*1*).

Selected vernacular names

It is most commonly known as "onion". Basal, basl, cebolla, cebolla morada, cepa bulb, cepolla, cipolla, common onion, cu hanh, hom hua yai, hom khaao, hom yai, hu-t'sung, hu t'sung t'song, hua phak bhu, i-i-bsel, kesounni, khtim, Küchenzwiebel, l'oignon, loyon, Madras oignon, oignon, palandu, piyaj, piyaz, pyaz, pyaaz, ralu lunu, red globe onion, sibuyas, Spanish onion, tamanegi, umbi bawang merah, vengayan, yellow Bermuda onion, white globe onion, Zwiebel (*1–5*).

Description

A perennial herb, strong smelling when crushed; bulbs vary in size and shape from cultivar to cultivar, often depressed-globose and up to 20 cm in diameter; outer tunics membranous. Stem up to 100 cm tall and 30 mm in diameter, tapering from inflated lower part. Leaves up to 40 cm in height and 20 mm in diameter, usually almost semicircular in section and slightly flattened on upper side; basal in first year, in second year their bases sheathing the lower sixth of the stem. Spathe often 3-valved, persistent, shorter than the umbel. Umbel 4–9 cm in diameter, subglobose or hemispherical, dense, many-flowered; pedicels up to 40 mm, almost equal. Perianth stellate; segments 3–4.5 × 2–2.5 mm, white, with green stripe, slightly unequal, the outer ovate, the inner oblong, obtuse or acute. Stamens exserted; filaments 4–5 mm, the outer subulate, the inner with an expanded base up to 2 mm wide and bearing short teeth on each side. Ovary whitish. Capsule about 5 mm, $2n = 16$ (*6*).

Plant material of interest: fresh or dried bulbs

General appearance

Macroscopically, Bulbus Allii Cepae varies in size and shape from cultivar to cultivar, 2–20 cm in diameter; flattened, spherical or pear-shaped; white or coloured (*7*).

Organoleptic properties

Odour strong, characteristic alliaceous; taste strong; crushing or cutting the bulb stimulates lachrymation.

Microscopic characteristics

The external dried leaf scales of the bulbs show a large-celled epidermis with lightly spotted cell walls; the cells are elongated longitudinally. The underlying hypodermis runs perpendicular to the epidermis and contains large calcium oxalate crystals bordering the cell walls. The epidermis of the fleshy leaf scales resembles that of the dried leaf scales, and the epidermal cells on the dorsal side are distinctly longer and more elongated than the epidermal cells on the ventral side. Large calcium oxalate crystals are found in the hypodermis; stomata rare; large cell nuclei conspicuous; and spiral vessel elements occur in the leaf mesophyll (*8*).

Powdered plant material

Contains mainly thin-walled cells of the mesophyll with broken pieces of spiral vessel elements; cells containing calcium oxalate crystals are scarce (*8*).

Geographical distribution

Bulbus Allii Cepae ("onion") is probably indigenous to western Asia, but it is commercially cultivated worldwide, especially in regions of moderate climate (*1*).

General identity tests

Macroscopic inspection, microscopic characteristics and microchemical examination for organic sulfur compounds (*9*); and thin-layer chromatographic analysis for the presence of cysteine sulfoxides (*10*, *11*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Bulbus Allii Cepae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*12*–*14*). Preparations for oral 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 6% (*3*).

Acid-insoluble ash

Not more than 1.0% (*3*).

Water-soluble extractive

Not more than 5.0% (*3*).

Alcohol-soluble extractive

Not more than 4.0% (*3*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Bulbus Allii Cepae is not more than 0.05 mg/kg (*14*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*12*) and guidelines for predicting dietary intake of pesticide residues (*15*).

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 (*12*).

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 (*12*).

Other purity tests

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

Chemical assays

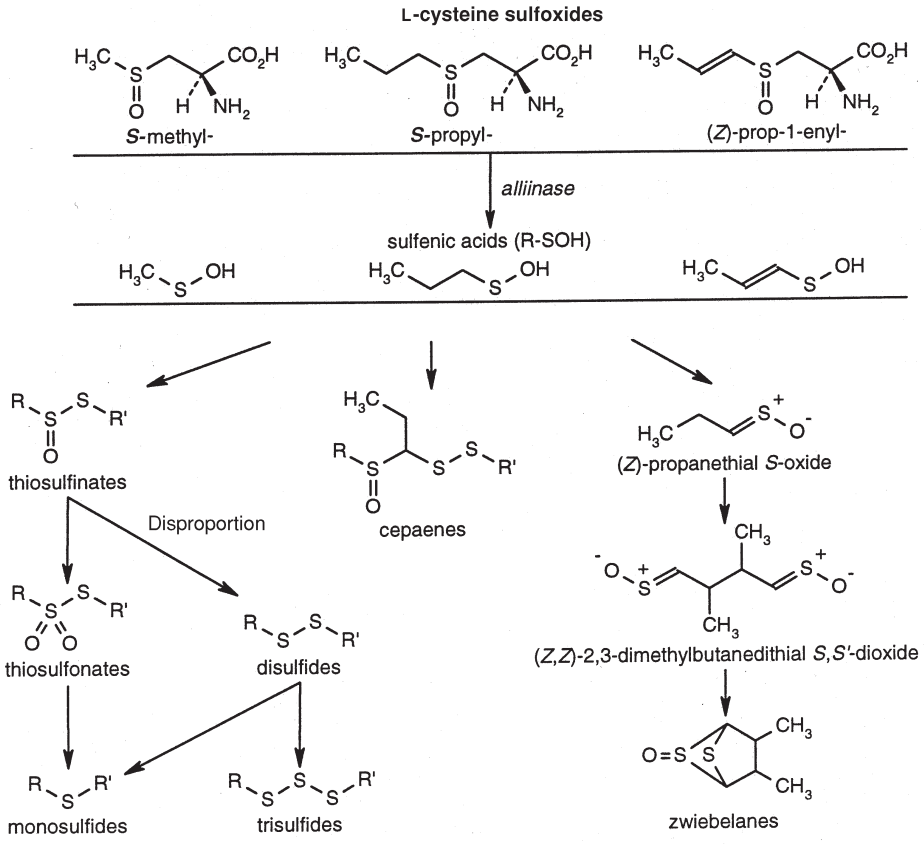
Assay for organic sulfur constituents, cysteine sulfoxides and sulfides by means of high-performance liquid chromatographic (*16*, *17*) or gas–liquid chromatographic (*18*) methods, respectively. Quantitative levels to be established by appropriate national authority.

Major chemical constituents

Sulfur- and non-sulfur-containing chemical constituents have been isolated from Bulbus Allii Cepae; the sulfur compounds are the most characteristic (*1*, *4*, *7*).

The organic sulfur compounds of Bulbus Allii Cepae, including the thiosulfinates, thiosulfonates, cepaenes, *S*-oxides, *S*,*S*′-dioxides, monosulfides,

disulfides, trisulfides, and zwiebelanes occur only as degradation products of the naturally occurring cysteine sulfoxides (e.g. (+)-*S*-propyl-L-cysteine sulfoxide). When the onion bulb is crushed, minced, or otherwise processed, the cysteine sulfoxides are released from compartments and contact the enzyme alliinase in adjacent vacuoles. Hydrolysis and immediate condensation of the reactive intermediate (sulfenic acids) form the compounds as indicated below (*1*). The odorous thiosulphonates occur (in low concentrations) only in freshly chopped onions, whereas the sulfides accumulate in stored extracts or steam-distilled oils. Approximately 90% of the soluble organic-bound sulfur is present as γ-glutamylcysteine peptides, which are not acted on by alliinase. They function as storage reserve and contribute to the germination of seeds. However, on prolonged storage or during germination, these peptides are acted on by γ-glutamyl transpeptidase to form alk(en)yl-cysteine sulfoxides, which in turn give rise to other volatile sulfur compounds (*1*).



Dosage forms

Fresh juice and 5% and 50% ethanol extracts have been used in clinical studies (*1*). A "soft" extract is marketed in France but is not recognized as a drug by French authorities (*7*). Dried Bulbus Allii Cepae products should be stored in well-closed containers, protected from light, moisture, and elevated temperature. Fresh bulbs and juice should be refrigerated (2–10 °C).

Medicinal uses

Uses supported by clinical data

The principal use of Bulbus Allii Cepae today is to prevent age-dependent changes in the blood vessels, and loss of appetite (*19*).

Uses described in pharmacopoeias and in traditional systems of medicine

Treatment of bacterial infections such as dysentery, and as a diuretic (*2*, *7*). The drug has also been used to treat ulcers, wounds, scars, keloids (*3*), and asthma (*20*, *21*). Bulbus Allii Cepae has also been used as an adjuvant therapy for diabetes (*4*, *22*, *23*).

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

As an anthelminthic, aphrodisiac, carminative, emmenagogue, expectorant, and tonic (*3*), and for the treatment of bruises, bronchitis, cholera, colic, earache, fevers, high blood pressure, jaundice, pimples, and sores (*3*).

Pharmacology

Experimental pharmacology

An aqueous extract or the juice of Bulbus Allii Cepae inhibited the *in vitro* growth of *Escherichia coli, Serratia marcescens, Streptococcus* species, *Lactobacillus odontolyticus, Pseudomonas aeruginosa*, and *Salmonella typhosa* (*24–28*). A petroleum ether extract of Bulbus Allii Cepae inhibited the *in vitro* growth of *Clostridium paraputrificum* and *Staphylococcus aureus* (*24*). The essential oil has activity against a variety of fungi including *Aspergillus niger*, *Cladosporium werneckii*, *Candida albicans*, *Fusarium oxysporium*, *Saccharomyces cerevisiae*, *Geotrichum candidum*, *Brettanomyces anomalus*, and *Candida lipolytica* (*5*, *29*).

The hypoglycaemic effects of Bulbus Allii Cepae have been demonstrated *in vivo*. Intragastric administration of the juice, a chloroform, ethanol, petroleum ether (0.25 g/kg) or water extract (0.5 ml), suppressed alloxan-, glucose- and epinephrine-induced hyperglycaemia in rabbits and mice (*30–35*).

Inhibition of platelet aggregation by Bulbus Allii Cepae has been demonstrated both *in vitro* and *in vivo*. An aqueous extract inhibited adenosine diphosphate-, collagen-, epinephrine- and arachidonic acid-induced platelet

aggregation *in vitro* (*36*, *37*). Platelet aggregation was inhibited in rabbits after administration of the essential oil, or a butanol or chloroform extract of the drug (*38–40*). An ethanol, butanol or chloroform extract or the essential oil (10–60 μg/ml) of the drug inhibited aggregation of human platelets *in vitro* (*41*, *42*) by decreasing thromboxane synthesis (*39*). Both raw onions and the essential oil increased fibrinolysis in *ex vivo* studies on rabbits and humans (*1*). An increase in coagulation time was also observed in rabbits (*1*).

Intragastric administration of the juice or an ether extract (100 mg/kg) of the drug inhibited allergen- and platelet activating factor-induced allergic reactions, but not histamine- or acetylcholine-induced allergenic responses in guinea-pigs (*43*). A water extract of the drug was not active (*43*). A chloroform extract of Bulbus Allii Cepae (20–80 mg/kg) inhibited allergen- and platelet aggregation factor-induced bronchial obstruction in guinea-pigs (*44*). The thiosulphinates and cepaenes appear to be the active constituents of Bulbus Allii Cepae (*1*).

Both ethanol and methanol extracts of Bulbus Allii Cepae demonstrated diuretic activity in dogs and rats after intragastric administration (*45*, *46*).

Antihyperlipidaemic and anticholesterolaemic activities of the drug were observed after oral administration of minced bulbs, a water extract, the essential oil (100 mg/kg), or the fixed oil to rabbits or rats (*47–52*). However, one study reported no significant changes in cholesterol or lipid levels of the eye in rabbits, after treatment of the animals for 6 months with an aqueous extract (20% of diet) (*53*).

Oral administration of an ethanol extract of the drug to guinea-pigs inhibited smooth muscle contractions in the trachea induced by carbachol and inhibited histamine-, barium chloride-, serotonin-, and acetylcholine-induced contractions in the ileum (*20*).

Topical application of an aqueous extract of Bulbus Allii Cepae (10% in a gel preparation) inhibited mouse ear oedema induced by arachidonic acid (*54*). The active antiallergic and anti-inflammatory constituents of onion are the flavonoids (quercetin and kaempferol) (*55*). The flavonoids act as anti-inflammatory agents because they inhibit the action of protein kinase, phospholipase A2, cyclooxygenase, and lipoxygenase (*56*), as well as the release of mediators of inflammation (e.g. histamine) from leukocytes (*57*).

In vitro, an aqueous extract of Bulbus Allii Cepae inhibited fibroblast proliferation (*58*). A 0.5% aqueous extract of onion inhibited the growth of human fibroblasts and of keloidal fibroblasts (enzymically isolated from keloidal tissue) (*59*). In a comparative study, an aqueous extract of Bulbus Allii Cepae (1–3%) inhibited the proliferation of fibroblasts of varying origin (scar, keloid, embryonic tissue). The strongest inhibition was observed with keloid fibroblasts (65–73%) as compared with the inhibition of scar and embryonic fibroblasts (up to 50%) (*59*). In human skin fibroblasts, both aqueous and chloroform onion extracts, as well as thiosulfinates, inhibited the platelet-derived growth factor-stimulated chemotaxis and proliferation of these cells (*60*). In addition, a protein fraction isolated from an onion extract exhibited antimitotic activity (*61*).

Clinical pharmacology

Oral administration of a butanol extract of Bulbus Allii Cepae (200 mg) to subjects given a high-fat meal prior to testing suppressed platelet aggregation associated with a high-fat diet (*62*).

Administration of a butanol extract to patients with alimentary lipaemia prevented an increase in the total serum cholesterol, β-lipoprotein cholesterol, and β-lipoprotein and serum triglycerides (*63*, *64*). A saponin fraction (50 mg) or the bulb (100 mg) also decreased serum cholesterol and plasma fibrinogen levels (*65*, *66*). However, fresh onion extract (50 g) did not produce any significant effects on serum cholesterol, fibrinogen, or fibrinolytic activity in normal subjects (*67*, *68*).

Antihyperglycaemic activity of Bulbus Allii Cepae has been demonstrated in clinical studies. Administration of an aqueous extract (100 mg) decreased glucose-induced hyperglycaemia in human adults (*69*). The juice of the drug (50 mg) administered orally to diabetic patients reduced blood glucose levels (*22*). Addition of raw onion to the diet of non-insulin-dependent diabetic subjects decreased the dose of antidiabetic medication required to control the disease (*70*). However, an aqueous extract of Bulbus Allii Cepae (200 mg) was not active (*71*).

The immediate and late cutaneous reactions induced by injection of rabbit anti-human IgE-antibodies into the volar side of the forearms of 12 healthy volunteers were reduced after pretreatment of the skin with a 50% ethanol onion extract (*1*). Immediate and late bronchial obstruction owing to allergen inhalation was markedly reduced after oral administration of a 5% ethanol onion extract 1 hour before exposure to the allergen (*1*).

In one clinical trial in 12 adult subjects, topical application of a 45% ethanolic onion extract inhibited the allergic skin reactions induced by anti-IgE (*72*).

Contraindications

Allergies to the plant. The level of safety of Bulbus Allii Cepae is reflected by its worldwide use as a vegetable.

Warnings

No warnings have been reported.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Bulbus Allii Cepae is not mutagenic *in vitro* (*73*).

Other precautions

No general precautions have been reported, and no precautions have been reported concerning drug interactions, drug and laboratory test interactions,

nursing mothers, paediatric use, or teratogenic or non-teratogenic effects on pregnancy.

Adverse reactions

Allergic reactions such as rhinoconjunctivitis and contact dermatitis have been reported (*74*).

Posology

Unless otherwise prescribed: a daily dosage is 50 g of fresh onion or 20 g of the dried drug; doses of preparations should be calculated accordingly (*14*).

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