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Aristolochia

Serpentaria.

NOTE. *Aristolochia clematitis* has also been known as asarabacca (p.2261).

Pharmacopoeias. *Chin.* allows various species of *Aristolochia*.

Profile

Aristolochia spp. (birthworts) including *A. clematitis* and *A. ringens (A. brasiliensis)* have been used in herbal medicine.

Serpentary (serpentaria) is the dried rhizome and roots of *Aristolochia serpentaria* (Virginian snakeroot) and of *A. reticulata* (Texan snakeroot) (Aristolochiaceae). Snakeroot is also used as a common name to describe poisonous *Eupatorium* spp. Preparations of serpentary have been used as bitters. The active ingredient is aristolochic acid, which has been tried in a number of inflammatory disorders, mainly in folk medicine; the sodium salt of aristolochic acid has also been used. However, there is concern over such use since aristolochic acid has been reported to be carcinogenic and nephrotoxic.

Chinese medicine has employed various species of *Aristolochia* including *A. contorta*, *A. debilis* (but see under Adverse Effects, below), and *A. manshuriensis*. The terms Mu Tong and Fangji have been used for *Aristolochia* spp. in traditional medicine.

Adverse effects. Progressive interstitial fibrosis of the kidney related to a slimming regimen containing Chinese herbs had been reported in 70 patients in Belgium by 1993; 30 of these patients had terminal renal failure.[1] Renal failure has also been reported[2] in 2 patients in the UK after ingestion of Chinese herbal medicines that were later found to contain aristolochic acid, a known nephrotoxin;[3] one of these patients subsequently developed invasive urothelial carcinoma.[4] Inadvertent ingestion of aristolochic acid can originate as a result of the substitution of *Aristolochia* spp. (probably *A. manshuriensis*) for other innocuous herbal substances;[2,5] the Belgian cases were probably as a result of substitution of *A. fangchi* extracts for *Stephania tetrandra*.[1] As a result of these cases, the UK MCA issued a permanent ban on *Aristolochia* preparations in 1999. Similar bans have been made in several other countries;[3] in 2004, the Chinese regulatory authority also banned the use of *A. fangchi* and *A. debilis* in traditional medicine formulations. Examination of 39 patients in Belgium with nephropathy associated with *A. fangchi* ingestion had revealed 18 cases of urothelial carcinoma and evidence of mild to moderate dysplasia in 19 patients.[6] There had appeared to be a higher risk of carcinoma with total doses of *A. fangchi* in excess of 200 g.

Aristolochic acid has been proposed as the cause of endemic (Balkan) nephropathy,[7] which is confined to a very specific rural geographical distribution and first described in the 1950s. Data supporting this hypothesis included findings of DNA damage linked to aristolochic acid in kidney samples from affected patients, as well as renal failure in horses who had grazed in the local fields. *Aristolochia clematitis* is endemic to the region and has been found in fields cultivated for wheat grain. It is possible that the local population could be exposed to toxic amounts of aristolochic acid over time from bread made with grain contaminated with *A. clematitis* seeds.

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Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Euserpina Cellulite.

Multi-ingredient: ***S.Afr.:*** Borstol Cough Remedy.

Arnica

Árnica; Arnica, fleur d' (arnica flower); Arnicae Anthodium; Arnicae flos (arnica flower); Arnikablomma (arnica flower); Arnikinkukka (arnica flower); Arnikový květ (arnica flower); Arnikų žiedai (arnica flower); Hegyi árnika virág (arnica flower); Koszyczek arniki (arnica flower); Leopard's Bane; Mountain Tobacco; Wolf's Bane; Wolfsbane.

NOTE. Wolfsbane is also used as a common name for aconite (p.2246).

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Arnica Flower; Arnica Flos). It consists of the whole or partially broken, dried flowerheads of *Arnica montana*. It contains not less than 0.4% w/w of total sesquiterpene lactones expressed as dihydrohelenalin tiglate, calculated with reference to the dried drug. It has an aromatic odour. Protect from light.

Profile

Arnica is generally used in the form of the flowerheads of *Arnica montana* (Compositae).

Arnica flower is irritant to mucous membranes and when ingested has produced severe symptoms including gastrointestinal and nervous system disturbances, both tachycardia and bradycardia, and collapse. Tincture of arnica may cause dermatitis when applied to the skin of sensitive persons.

Preparations of arnica flower and arnica root are used as astringents for topical application to unbroken skin in conditions such as sprains and bruises; such preparations are not considered suitable for internal use. Arnica flowers are the source of arnica oil, which has been used similarly.

Herbal preparations containing arnica are available for oral use.

Homoeopathy. Arnica has been used in homoeopathic medicines under the following names: Arnica montana; Arnica, Flos; Arnica montana e flore; Arnica montana ex herba; Arnica, Planta tota; Arnica montana ex planta tota; Arn. mont. Some homoeopathic preparations are available for oral use.

◊ References.

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Preparations

Ph. Eur.: Arnica Tincture.

Proprietary Preparations (details are given in Part 3)

Arg.: Herbaccion Desinflamante†; ***Austral.:*** Sports Ice Bruising Relief; ***Belg.:*** Arnican; ***Chile:*** Arnikaderm; ***Fr.:*** Arnican; Pharmadose teinture d'arnica; ***Ger.:*** Arnikatinktur; Arthrosenex AR; Doc; Enelbin-Salbe; Hyzum N†; Vasotonin†; ***Mex.:*** Balsamo Nordin; Estimul; ***Port.:*** Arnigel; ***Singapore:*** SinEccH; ***UK:*** Arnicare; Atrogel.

Multi-ingredient: ***Arg.:*** Fluido; ***Austral.:*** Joint & Muscle Cream; Percutane; ***Austria:*** Arnicet; Asthmatee EF-EM-ES; Berggeist; Cional; Dynexan; Heparin Comp; Rheuma; Sportino Akut†; ***Belg.:*** Älgi-Cool; Purigel Crisp; Purigel NF; ***Braz.:*** Dermol†; Traumed†; ***Chile:*** Lefkaflam; Matikomp; ***Cz.:*** Arnidol; Heparin-Gel†; ***Fr.:*** Arnicadol; Creme Rap; Decramp; Dermocica; Evarose; Lelong Contusions†; ***Ger.:*** Arnikamill†; Cefawell†; Combudoron; Dolo-cyl; Essaven Sport†; Gothaplast Rheumamed AC; Heparin Comp†; Heparin Kombi-Gel†; Heusin†; Lindofluid N; Retterspitz Ausserlich; Retterspitz Quick; Rhoival†; Sportino Akut; Stullmaton†; Trauma-cyl; Varicylum-S; Venengel†; Vitosal†; ***Hong Kong:*** New Patecs A; ***Ital.:*** Flebolider; Flodolor; Venalta; ***Malaysia:*** Arnica Comp†; ***Mex.:*** Reudol; ***Pol.:*** Arcalen; Arnisol; Dentosept; Dentosept A; Emorect; Escalar; Prostapol; Reumobonisol; Stomatosol; Uroprost; Venoforton; ***S.Afr.:*** Arnica Massage Oil; Combudoron; Dynexan; Lotio Pruni Comp cum Cupro; Muscle Rub; Wecesin; ***Spain:*** Arnicon†; Encialina†; ***Switz.:*** Combudoron; Eubucal†; Euceta avec camomille et arnica; Fortacet; GU Eau†; Onguent aux herbes Keller; Perskindol Cool Arnica; Topaceta; Wecesin†; ***UK:*** Hansaplast Herbal Heat Plaster; Profelan; ***Venez.:*** Andantol Jalea; Biomicovo†; Gelsem.

Arsenic Trioxide *(USAN)*

Acidum Arsenicosum Anhydricum; Arseni Trioxydum; Arsenic; Arsenic Oxide; Arsénico, trióxido de; Arsenicum Album; Arsénieux, anhydride; Arsenii trioxidum; Arsenious Acid; Arsenous Oxide; White Arsenic. Diarsenic trioxide.

As_2O_3 = 197.8.

CAS — 1327-53-3 (arsenic trioxide); 7784-45-4 (arsenic triiodide).

ATC — L01XX27.

ATC Vet — QL01XX27.

Pharmacopoeias. In *Jpn.*

Eur. (see p.vii) includes a form for homoeopathic preparations.

Ph. Eur. 6.2 (Arsenious Trioxide for Homoeopathic Preparations; Arsenii Trioxidum ad Praeparationes Homoeopathicae). A white or almost white powder. Practically insoluble to sparingly soluble in water; it dissolves in solutions of alkali hydroxides and carbonates.

Adverse Effects

The toxicity of arsenic compounds varies according to chemical composition, solubility, and valency. Inorganic arsenic compounds are much more toxic than organic compounds and elemental arsenic is the least toxic. Toxicity increases with increasing solubility, and trivalent (arsenite) compounds are more toxic than pentavalent (arsenate) compounds. Arsenic exerts its effects through a variety of pathophysiological mechanisms such as induction of oxidative stress and binding to sulphydryl groups in enzymes, and it has the potential to affect most of the major organ systems in the body; it also induces alteration in gene expression.

Acute poisoning. Estimates of lethal and toxic oral doses vary: the lethal dose of arsenic trioxide has been reported to be around 100 to 300 mg; a dose of 1 mg/kg of arsenic may be lethal in children; acute toxic doses of arsenic compounds have been reported to range from 1 mg to 10 g. Symptoms of acute poisoning occur within 30 minutes to several hours after ingestion and food delays the onset.

Early features of acute arsenic poisoning following ingestion involve the gastrointestinal tract with common symptoms of a metallic or garlic taste, a burning sensation in the mouth, dysphagia, abdominal pain, severe nausea, projectile vomiting, haemorrhagic gastritis, and profuse 'rice-water' diarrhoea leading to hypovolaemic shock; the breath may have an odour of garlic. In the absence of adequate treatment, death can occur within 24 hours of a severely toxic dose. Absorption of arsenic may produce multisystem toxicity days or weeks later, which could include cardiomyopathy, anaemia, leucopenia, skin disorders, acute respiratory distress syndrome, hepatitis, renal failure, encephalopathy, and peripheral polyneuropathy.

Arsenic compounds are irritant and corrosive when inhaled or in contact with the skin or eyes; acute systemic effects may occur after inhalation or skin contact.

Chronic poisoning. Arsenic is widely distributed in the environment: the smelting industry (non-ferrous metals) is a major industrial source of arsenic contamination in the soil, water, and air; mining residues and arsenical pesticides and wood preservatives also contribute to soil and water contamination. Seafood is a source of organic arsenic. Occupational exposure is a potential cause of chronic arsenic toxicity but in the general population, food and drinking water is usually the source of arsenic.

Chronic arsenic poisoning or occupational exposure typically produces varied skin disorders appearing over 1 to 10 years, particularly hyperkeratosis, especially affecting the palms and soles, and changes in skin pigmentation. Transverse white lines (Mee's lines) may appear in the nails several weeks after absorption. Gastrointestinal disturbances may occur, although are less likely with chronic exposure. Hypertension, cardiovascular disorders, and diabetes mellitus have been associated with chronic arsenic poisoning. Jaundice may occur as a result of hepatomegaly and portal hypertension may eventually develop. Encephalopathy and peripheral neuropathies may also occur. Arsenic is toxic to the bone marrow and produces a wide range of blood disorders including leucopenia and aplastic anaemia. Chronic exposure to arsenic has been associated with neoplasms of the skin, lungs, bladder, liver, and kidney. Chronic inhalation of arsenic salts may result in perforation of the nasal septum.

Adverse effects of therapeutic use. Reported adverse effects of arsenic trioxide therapy in patients with acute promyelocytic leukaemia (APL) include leucocytosis, neutropenia, raised liver enzyme values, gastrointestinal disturbances, fatigue, oedema, hyperglycaemia, hypokalaemia, dyspnoea, cough, skin rashes, pruritus, pyrexia, headaches, paraesthesia, and dizziness. Prolongation of the QT interval and other cardiac arrhythmias have occurred. The so-called 'leukocyte activation syndrome' ('APL differentiation syndrome') similar to one that develops with tretinoin therapy (see Retinoic Acid Syndrome, p.1618) has occurred in some patients. Sudden death has been reported in a few patients.

◊ References,[1-8] including discussion of epidemic toxicity due to arsenic-contaminated drinking water.[4,6-8]

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Adulteration. Arsenical compounds have reportedly been used to "cut" cocaine and symptoms of arsenic poisoning may occur in cocaine abusers.[1] Toxicity due to the presence of arsenic in various ethnic remedies has also been reported.[2-4]

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