Herba Ephedrae

Definition
Herba Ephedrae consists of the dried stem or aerial part of *Ephedra sinica* Stapf or other ephedrine-containing *Ephedra* species (Ephedraceae) (1–5).

Synonyms
None.

Selected vernacular names
Amsania, budshur, chewa, Chinese ephedra, ephédra, horsetail, hum, huma, joint fir, khama, ma hoàng, ma huang, máhuáng, mao, maoh, mao-kon, môc tac ma hoàng, mu-tsei-ma-huang, phok, san-ma-huang, shrubby, soma, song tuê ma hoàng, trung aa hoàng, tsao-ma-huang, tutgantha (4–10).

Description
Erect or prostrate, green, almost leafless shrub, 20–90 cm high. Branches erect, short, glaucous green, somewhat flat, 1.0–1.5 mm in diameter, with small sparse longitudinal striae, fasciated at the nodes; nodes reddish brown; internode 2.5–5.5 cm long × 2 mm in diameter. Small triangular leaves opposite, reduced to scales, barely 2 mm. Flowers in summer, unisexual, dioecious; male flowers pedunculate or nearly sessile, grouped in catkins composed of 4 to 8 pairs of flowers with about 8 anthers; female flowers biflorous, pedunculate with 3 or 4 pairs of bracts, the naked ovule surrounded by an urn-shaped perianth sheath, fruiting with often fleshy red succulent bracts, 2-seeded (4, 7, 11).

Plant material of interest: stem or aerial part

General appearance
Macroscopically, Herba Ephedrae occurs as thin cylindrical or ellipsoidal cylinder, 1–2 mm in diameter; 3.5–5.5 cm in length of internode; light green to yellow-green; numerous parallel vertical furrows on the surface; scaly leaves at the node portion; leaves, 2–4 mm in length, light brown to brown in colour, usually opposite at every node, adhering at the base to form a tubular sheath around the stem. Under a magnifying glass, the transverse section of the stem appears as circle and ellipse, the outer portion greyish green to yellow-green in
colour, and the centre filled with a red-purple substance or hollow. When fractured at an internode, the outer part is fibrous and easily split vertically (1).

**Organoleptic properties**
Odour, slight; taste, slightly bitter and astringent, giving a slight sensation of numbness on the tongue (1).

**Microscopic characteristics**
The epidermal cells of the stem are covered with a moderately thick granular cuticle; the cells are polygonal or subrectangular, axially elongated, having straight anticlinal walls. The stomata are few and are of the ranunculaceous type with lignified appendages. The epidermis of the scaly leaf is covered with smooth (upper) or warty (lower) cuticle and consists of subrectangular to polygonal cells, having straight or sometimes slightly beaded anticlinal walls; few stomata are present resembling those of stem. The epidermis of the apical and marginal regions of the scaly leaf shows short papillae-like outgrowths. Chlorenchymatous palisade-like cells form the outer zone of the cortex; rounded ordinary parenchymatous cells form the inner zone of the cortex. Cortical parenchyma and pith cells contain an amorphous reddish brown substance. Non-lignified or lignified hypodermal and pericyclic fibres, which have thick walls, bear slit-like pits and blunt, slightly tapering, occasionally forked ends. The vessels of the secondary xylem of the stem are lignified with bordered pits, having rounded or oval apertures. The vessel segments have much inclined end walls, bearing foraminate perforation plates. The tracheids and fibrous tracheids of secondary xylem of the stem are lignified with bordered pits having oval or slit-like apertures. The fibres of the scaly leaf are lignified, usually irregular or nearly straight, having moderately thick walls and blunt or sometimes forked ends. Few, small, rounded, simple and compound starch granules with indistinct hilum are present in cortical parenchyma, pith, and medullary ray cells. Few, small prisms of calcium oxalate are present in the cortical parenchyma (4).

**Powdered plant material**
Powdered Herba Ephedrae is greyish green. Numerous thick fragments of cutinized outer walls of epidermis vary from colourless to varying shades of brown or red; numerous fragments of sclerenchyma fibres with extremely thickened, non-lignified to lignified walls, narrow, frequently indistinct lumina and sharp pointed ends; fragments of vascular tissue showing tracheids with bordered pores and occasional spiral and pitted tracheae; numerous chlorenchyma cells; starch grains simple, spheroidal to occasionally ovate, averaging up to 1.2 μm but occasionally up to 20 μm; fragments of epidermis with rectangular cells and granular contents, some with sunken elliptical stomata; fragments of
lignified or non-lignified pith parenchyma, some of the cells showing mucilage sacs; papillae; granules of calcium oxalate \( (4, 6) \).

**Geographical distribution**

*Ephedra* species are found in Afghanistan, Central America, China, India, regions of the Mediterranean, Mongolia, and North America \( (4, 6–12) \).

**General identity tests**

Macroscopic and microscopic examinations and microchemical tests for the presence of alkaloids with Mayer’s reagent \( (1–5, 7) \).

**Purity tests**

**Microbiology**

The test for *Salmonella* spp. in *Herba Ephedrae* products should be negative. The maximum acceptable limits for other microorganisms are as follows \( (13–15) \). For preparation of decoction: aerobic bacteria—not more than \( 10^7 \) g; fungi—not more than \( 10^6 \) 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**

Woody stems, not more than 5% \( (1) \). Does not contain stems of Equisetaceae or Gramineae plants, nor any other foreign matter \( (1) \).

**Total ash**

Not more than 9% \( (3) \).

**Acid-insoluble ash**

Not more than 2% \( (1) \).

**Moisture**

Not more than 9% \( (3) \).

**Pesticide residues**

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for *Herba Ephedrae* is not more than \( 0.05 \) mg/kg \( (15) \). For other pesticides, see WHO guidelines on quality control methods for medicinal plants \( (13) \) 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 (13).

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 (13).

Other purity 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 0.7% total alkaloids, calculated as ephedrine by high-performance liquid chromatography in the Japanese pharmacopoeia; or not less than 0.8% of total alkaloids, calculated as ephedrine in the Chinese pharmacopoeia (1, 2).

Thin-layer (17), gas-liquid (18) or high-performance liquid (19) chromatographic analysis for ephedrine and related alkaloids are available.

Major chemical constituents
The major active principle found in Herba Ephedrae is (−)-ephedrine in concentrations of 40–90% of the total alkaloid fraction, accompanied by (−)-norephedrine. Other trace alkaloids in the alkaloid complex include (−)-pseudoephedrine, (−)-norpseudoephedrine, (−)-methylephedrine and (−)-methylpseudoephedrine. The total alkaloid content can exceed 2% depending on the species (20). Not all Ephedra species contain ephedrine or alkaloids.
Dosage forms
Powdered plant material; extracts and other galenicals. Store in well closed, light-resistant containers.

Medicinal uses

Uses supported by clinical data
Herba Ephedrae preparations are used in the treatment of nasal congestion due to hay fever, allergic rhinitis, acute coryza, common cold, and sinusitis. The drug is further used as a bronchodilator in the treatment of bronchial asthma (4, 8, 10, 21–23).

Uses described in pharmacopoeias and in traditional systems of medicine
Herba Ephedrae has been used for the treatment of urticaria, enuresis, narcolepsy, myasthenia gravis, and chronic postural hypotension (4, 8, 22, 23).

Uses described in folk medicine, not supported by experimental or clinical data
Other medical uses claimed for Herba Ephedrae preparations include its use as an analgesic, an antiviral agent, an antitussive and expectorant, an antibacterial, and an immune stimulant (10, 24, 25).

Clinical pharmacology
Two of the main active constituents of Herba Ephedrae, ephedrine and pseudoephedrine, are potent sympathomimetic drugs that stimulate α-, β₁- and β₂- adrenoceptors (22, 23). Pseudoephedrine’s activity is similar to ephedrine, but its hypertensive effects and stimulation of the central nervous system are somewhat weaker. Part of ephedrine’s peripheral action is due to the release of norepinephrine, but the drug also directly affects receptors. Tachyphylaxis develops to its peripheral actions, and rapidly repeated doses become less effective owing to the depletion of norepinephrine stores (22).

Cardiovascular actions
Like epinephrine (adrenaline), ephedrine excites the sympathetic nervous system, causing vasoconstriction and cardiac stimulation. Ephedrine differs from epinephrine in that it is orally active, has a much longer duration of action, and has more pronounced activity in the central nervous system, but is much less potent (22, 23). The drug stimulates the heart rate, as well as cardiac output, and increases peripheral resistance, thereby producing a lasting rise in blood pressure. The cardiovascular effects of ephedrine persist up to ten times as long as
those of epinephrine (22). Ephedrine elevates both the systolic and diastolic pressures and pulse pressure. Renal and splanchnic blood flows are decreased, while coronary, cerebral, and muscle blood flows are increased (22, 23).

**Bronchodilator and nasal decongestant**

Ephedrine, like epinephrine, relaxes bronchial muscles and is a potent bronchodilator owing to its activation of the $\beta$-adrenoceptors in the lungs (22, 23). Bronchial muscle relaxation is less pronounced but more sustained with ephedrine than with epinephrine. As a consequence, ephedrine should be used only in patients with mild cases of acute asthma and in chronic cases that require maintenance medication. Ephedrine, like other sympathomimetics with $\alpha$-receptor activity, causes vasoconstriction and blanching when applied topically to nasal and pharyngeal mucosal surfaces (22, 23). Continued, prolonged use of these preparations (>5 days) may cause rebound congestion and chronic rhinitis (26). Both ephedrine and pseudoephedrine are useful orally as nasal decongestants in cases of allergic rhinitis, but they may not be very effective for the treatment of nasal congestion due to colds.

**Central nervous system**

Mydriasis occurs after local application of ephedrine (3–5%) to the eye, but the effect lasts for only a few hours (22). Ephedrine is of little value as a mydriatic in the presence of inflammation. The activity of the smooth muscles of the uterus is usually reduced by ephedrine; consequently, the drug has been used to relieve the pain of dysmenorrhoea (22).

Ephedrine is a potent stimulator of the central nervous system. The effects of the drug may last for several hours after oral administration (23). Thus, preparations containing Herba Ephedrae have been promoted for use in weight reduction and thermogenesis (fat burning) (27, 28). The safety and effectiveness of these preparations is currently an issue of debate and requires further investigation (29).

Ephedrine stimulates the $\alpha$-adrenoceptors of the smooth muscle cells of the bladder base, which increases the resistance to the outflow of urine (23). Thus Herba Ephedrae has been used in the treatment of urinary incontinence and nocturnal enuresis.

**Contraindications**

Herba Ephedrae should not be administered to patients with coronary thrombosis, diabetes, glaucoma, heart disease, hypertension, thyroid disease, impaired circulation of the cerebrum, phaeochromocytoma, or enlarged prostate (10, 24, 23). Co-administration of Herba Ephedrae preparations with monoamine oxidase inhibitors is contraindicated as the combination may cause severe, possibly fatal, hypertension (23).
**Warnings**
Dosage should be reduced or treatment discontinued if nervousness, tremor, sleeplessness, loss of appetite or nausea occurs. Not for children under 6 years of age. Keep out of the reach of children (30). Continued, prolonged use may cause dependency.

**Precautions**

**General**
Insomnia may occur with continued use of Herba Ephedrae preparations (23).

**Drug interactions**
In combination with cardiac glycosides or halothane, may cause heart rhythm disturbances (21); with guanethidine, may cause an enhancement of sympathomimetic effect (21); with monoamine oxidase inhibitors, can cause severe, possibly fatal, hypertension (26); with ergot alkaloid derivatives or oxytocin, may increase risk of high blood pressure (21).

**Carcinogenesis, mutagenesis, impairment of fertility**
Extracts of Ephedra sinica are not mutagenic in the Salmonella/microsome reversion assay (31).

**Pregnancy: teratogenic effects**
Ephedra sinica did not have any teratogenic effects in vivo (32).

**Pregnancy: nonteratogenic effects**
Ephedra sinica is not abortifacient in rats (32). Clinical studies in humans are not available; therefore, use of the drug during pregnancy is not generally recommended.

**Nursing mothers**
There are no reliable studies on this subject. Therefore, nursing mothers should not take Herba Ephedrae without consulting a physician.

**Paediatric use**
Herba Ephedrae should not be administered to children under 6 years of age.

**Other precautions**
No information available concerning drug and laboratory test interactions.

**Adverse reactions**
In large doses Herba Ephedrae products can cause nervousness, headaches, insomnia, dizziness, palpitations, skin flushing and tingling, and vomiting (21).
The principal adverse effects of ephedrine and Herba Ephedrae are stimulation of the central nervous system, nausea, tremors, tachycardia, and urine retention (24). Continued, prolonged use (>3 days) of topical preparations containing Herba Ephedrae, for the treatment of nasal congestion, may cause rebound congestion and chronic rhinitis (26). Continued prolonged use of oral preparations may cause dependency (21).

**Posology**

Crude plant material: 1–6g for decoction daily (8, 21). Liquid extract (1:1 in 45% alcohol): 1–3ml daily (21). Tincture (1:4 in 45% alcohol): 6–8ml daily (21).

**References**

10. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, 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).
Folium Ginkgo

Definition
Folium Ginkgo consists of the dried whole leaf of Ginkgo biloba L. (Ginkgoaceae).

Synonyms
Pterophyllum salisburiensis Nelson, Salisburia adiantifolia Smith, Salisburia macrophylla C. Koch (1–4).

Selected vernacular names
Eun-haeng, gin-nan, ginkgo, ginkgo balm, ginkgo leaves, ginkyo, ginan, icho, ityo, kew tree, maidenhair tree, pei-wen, temple balm, yin guo, yinhsing (1–5).

Description
A monotypic dioecious plant that is the only living representative of the Ginkgoales. It has a grey bark, reaches a height of 35 m and a diameter of 3–4 m (sometimes up to 7 m), and has fan-like leaves that are deciduous, alternate, lengthily petiolate, bilobate, base wedge-shaped, 6–9 cm broad (sometimes up to 15–20 cm), turning yellow in autumn. Venation dichotomously branching, seemingly parallel. Staminate and ovulate strobili borne on separate trees; staminate strobili consisting of naked pairs of anthers in catkin-like clusters; ovulate strobili in the form of long, slender, fused stalks bearing a single naked ovule which is fertilized by motile sperm cells, developing into 2 seeds. Seeds yellow when mature, foul-smelling, drupe-like, the middle layer of integument becoming hard or stone-like, the outer layer fleshy (3, 4).

Plant material of interest: dried leaf
The kernel (nut, seed) is used in Chinese medicine (6, 7).

General appearance
The leaves are green, grey-yellow, brown or blackish; the upper side of a leaf may be somewhat darker than the underside. The leaves are fan-shaped, long-petioled and have two lobes with forked veins radiating from the petiole end (2, 4, 8).
Organoleptic properties
Ginkgo leaves have a weak characteristic odour (2, 4, 8).

Microscopic characteristics
Young leaves have abundant trichomes that become confined to the petiole base as the leaf ages. While the leaves have no midrib, dichotomous venation with regular, numerous branching parallel veins arises from two vascular strands within the petiole. Stomata occur almost exclusively on the lower surface of the leaf. The epidermis of the upper and underside of the leaf consists of undulated, irregular, mostly long extended cells. In the cross-section, the epidermal cells appear nearly isodiametric and from above appear to be slightly undulated, with the upper cells appearing larger. The outer walls of the epidermal cells are covered with a more or less thin layer of cuticle. In the area of vascular bundles there are remarkable long extended narrow cells with slightly undulated walls. Numerous druses of calcium oxalate occur near the vascular bundles (2, 4).

Powdered plant material
The colour of the powder agrees with that of the leaves. The powder shows fragments of the epidermis with wavelike indentations irregular in form with generally elongated cells; large stomal openings of the anisocytic type; markedly elongated, narrow cells with only weakly undulated walls in the vascular areas and without marked indentations. The equifacial mesophyll comprises excretory vesicles, secretory cells, and idioblasts, as well as intermittent calcium oxalate druses, in the region of the vascular fascicles (2, 8).

Geographical distribution
Native to China, but grown as an ornamental shade tree in Australia, south-east Asia, Europe, Japan, and the United States of America (1–3, 6). It is commercially cultivated in France and the United States of America (2).

General identity tests
Macroscopic and microscopic examinations (2, 8). Thin-layer chromatographic analysis for the presence of the characteristic flavonoids, ginkgolides, and bilobalide (9); high-performance liquid chromatographic analysis for flavonoids (10), ginkgolides, and bilobalide (2); and gas–liquid chromatographic evaluation of ginkgolides and bilobalide (11).

Purity tests
Microbiology
The test for Salmonella spp. in Folium Ginkgo should be negative. The maximum acceptable limits of other microorganisms are as follows (12–14). For preparation of decoction: aerobic bacteria—not more than 10^7/g; fungi—not
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more than $10^5$/g; *Escherichia coli*—not more than $10^7$/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 5% of twigs and not more than 2% of other foreign matter (15).

**Total ash**
Not more than 11% (15).

**Pesticide residues**
To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Folium Ginkgo 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 (16).

**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 (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**
Acid-insoluble ash, acid-insoluble extractive, chemical, and moisture tests to be established in accordance with national requirements.

**Chemical assays**
Flavonoids not less than 0.5% calculated as flavonol glycosides or 0.2–0.4% calculated as aglycones (17); also contains ginkgolides (0.06–0.23%) and bilobalide (up to 0.26%) (2, 17).

Qualitative and quantitative determination of flavonoid glycosides is carried out after hydrolysis to the aglycones kaempferol, quercetin, and isorhamnetin. The qualitative presence or absence of biflavones (17) is determined by high-performance liquid chromatography; and qualitative and quantitative determination of the diterpene ginkgolides and sesquiterpene bilobalide by high-performance liquid chromatography (2, 18) or gas-liquid chromatography (14).

Certain commercial products used for clinical and experimental biological studies, e.g. EGb 761 and LI 1370, do not contain biflavones.
Major chemical constituents

Folium Ginkgo contains a wide variety of phytochemicals, including alkanes, lipids, sterols, benzenoids, carotenoids, phenylpropanoids, carbohydrates, flavonoids, and terpenoids (18, 19). The major constituents are flavonoids of which mono-, di-, and tri-glycosides and coumaric acid esters that are based on the flavonols kaempferol and quercetin dominate. Lesser quantities of glycosides are derived from isorhamnetin, myricetin, and 3’-methylmyricetin. Nonglycosidic biflavonoids, catechins, and proanthocyanidins are also present (15). Characteristic constituents of this plant material are the unique diterpene lactones ginkgolides A, B, C, J, and M and the sesquiterpene lactone bilobalide (17). Representative structures of the major and characteristic constituents are presented below.
Dosage forms
Standardized extracts (dry extracts from dried leaves, extracted with acetone and water, drug:extract ratio 35–67:1) contain 22–27% flavone glycosides and 5–7% terpene lactones, of which approximately 2.8–3.4% consists of ginkgolides A, B, and C and 2.6–3.2% bilobalide. The level of ginkgolic acids is below 5 mg/kg. Coated tablets and solution for oral administration are prepared from standardized purified extracts (20, 21).

Medicinal uses
Uses supported by clinical data
Extracts as described above (Dosage forms) have been used for symptomatic treatment of mild to moderate cerebrovascular insufficiency (demential syndromes in primary degenerative dementia, vascular dementia, and mixed forms of both) with the following symptoms: memory deficit, disturbance in concentration, depressive emotional condition, dizziness, tinnitus, and headache (1, 3, 20–22). Such extracts are also used to improve pain-free walking distance in people with peripheral arterial occlusive disease such as intermittent claudication, Raynaud disease, acrocyanosis, and post-phlebitis syndrome, and to treat inner ear disorders such as tinnitus and vertigo of vascular and involutive origin (20, 23–27). Extracts and doses other than those described in Dosage forms and Posology are used for similar but milder indications (28, 29).

Uses described in pharmacopoeias and in traditional systems of medicine
None.

Uses described in folk medicine, not supported by experimental or clinical data
As a vermifuge, to induce labour, for the treatment of bronchitis, chronic rhinitis, chilblains, arthritis, and oedema (3, 5).

Pharmacology
Experimental pharmacology
Cerebrovascular insufficiency and peripheral vascular diseases
In vitro studies. A standardized extract of Ginkgo biloba (100 µg/ml) did not produce isometrically recordable contractions in isolated rabbit aorta but did potentiate the contractile effect of norepinephrine (30). Higher concentrations (EC50 ≈ 1.0 mg/ml) produced a concentration-dependent contraction that could be antagonized by the α-adrenoceptor-blocking agent phentolamine (30). Both cocaine and desipramine, inhibitors of catecholamine re-uptake, potentiated the contractile effect of norepinephrine but inhibited the contractile effects of a
standardized extract of *G. biloba* and tyramine (30). The results of these experiments indicate that the contractile action of *G. biloba* may be due to the release of catecholamines from endogenous tissue reserves, and this activity may explain some of the therapeutic effects of the drug in humans (e.g., improvement in cerebrovascular and peripheral vascular insufficiency) (1, 30). On the basis of experiments comparing the effects of an extract of *G. biloba*, phentolamine, propranolol, gallopamil, theophylline, and papaverine on the biphasic contractile response of norepinephrine in isolated rat aorta, researchers concluded that *G. biloba* had musculotropic action similar to that of papaverine (31). This activity was previously reported for the flavonoids quercetin, kaempferol, and isorhamnetin, isolated from the leaves of *G. biloba* (32). The flavonoids and papaverine both inhibit 3',5'-cyclic-GMP phosphodiesterase, which in turn induces endothelium-dependent relaxation in isolated rabbit aorta by potentiating the effects of endothelium-derived relaxing factors (1).

*In vitro* studies have demonstrated that *G. biloba* extracts scavenge free radicals (33–37). *Ginkgo* *biloba* extracts have been reported to reduce free radical-lipid peroxidation induced by NADPH-Fe$$^{3+}$$ systems in rat microsomes (33), and to protect human liver microsomes from lipid peroxidation caused by ciclosporin A (34). The extract also inhibits the generation of reactive oxygen radicals in human leukocytes treated with phorbol myristate acetate (35). The antioxidant action of *G. biloba* extract may prolong the half-life of endothelium-derived relaxing factor by scavenging superoxide anions (36, 37). Both the flavonoid and terpenoid constituents of *G. biloba* appear to aid the free-radical scavenging activity of the drug (37).

*Ginkgo* *biloba* extract protected against brain tissue hypoxic damage *in vitro*. The ginkgolides and bilobalide were responsible for the antihypoxic activity of the extract (38, 39). Ginkgolides A and B have been shown to protect rat hippocampal neurons against ischaemic damage, which may be due to their ability to act as antagonists to receptors for platelet-activating factor (PAF) (40–42).

*In vivo* studies. Oral administration of *G. biloba* extract protected rats against induced cerebral ischaemia (43–45). Intravenous perfusion of a *G. biloba* extract prevented the development of multiple cerebral infarction in dogs injected with fragments of an autologous clot into a common carotid artery (46). These data suggest that *G. biloba* extract, administered after clot formation, may have some beneficial effects on acute cerebral infarction or ischaemia caused by embolism (4). Other experiments demonstrated that animals treated with *G. biloba* extract survived under hypoxic conditions longer than did untreated controls (47, 48). Longer survival was due not only to significant improvements in cerebral blood flow, but also to an increase in the level of glucose and ATP (44, 48–50). Other studies have shown that a *G. biloba* extract devoid of ginkgolides but containing bilobalide had protective activity when administered intraperitoneally to mice with induced hypobaric hypoxia (51, 52). Intravenous infusion of *G. biloba* extract significantly increased pial arteriolar diameter in cats (53) and improved
cerebral blood flow in rats (53). The active constituents of *G. biloba* responsible for increasing cerebral blood flow appeared to be the non-flavonoid compounds (54); ginkgolide B may be responsible for this action owing to its PAF-antagonist activity (55, 56). Furthermore, intravenous administration of a standardized *G. biloba* extract and ginkgolide B to rats showed that the extract, but not ginkgolide B, decreased the brain’s use of glucose (57).

The constituents of *G. biloba* responsible for its anti-ischaemic activity remain undefined. The flavonoids, ginkgolides, and bilobalide have all been suggested, but it is possible that other constituents may be responsible.

An extract of *G. biloba* was effective in the *in vivo* treatment of cerebral oedema, a condition of excessive hydration of neural tissues owing to damage by neurotoxic agents (such as triethyltin) or trauma (58–60). Bilobalide appeared to play a significant role in the antioedema effect (61, 62). Oral or subcutaneous administration of an extract of *G. biloba* to rats with acute and chronic phases of adriamycin-induced paw inflammation partially reversed the increase in brain water, sodium, and calcium and the decrease in brain potassium associated with sodium arachidonate-induced cerebral infarction (63).

Mice treated with a standardized extract of *G. biloba* (100 mg/kg, orally for 4–8 weeks) showed improved memory and learning during appetitive operant conditioning (64).

**Vestibular and auditory effects**

*Ginkgo biloba* extract improved the sum of action potentials in the cochlea and acoustic nerve in cases of acoustically produced sound trauma in guinea-pigs (1, 65). The mechanism reduced the metabolic damage to the cochlea. Oral or parenteral administration of a standardized *G. biloba* extract to mice (2 mg/kg) improved the ultrastructure qualities of vestibular sensory epithelia when the tissue was fixed by vascular perfusion (66). Improvement was due to the effects of the drug on capillary permeability and general microcirculation (1, 66).

Positive effects on vestibular compensation were observed after administration of *G. biloba* extract (50 mg/kg intraperitoneally) to rats and cats that had undergone unilateral vestibular neurectomy (67, 68).

**Antagonism of platelet-activating factor (PAF)**

The ginkgolides, and in particular ginkgolide B, are known antagonists of PAF (69–73). PAF is a potent inducer of platelet aggregation, neutrophil degranulation, and oxygen radical production leading to increased microvascular permeability and bronchoconstriction. Intravenous injections of PAF induced transient thrombocytopenia in guinea-pigs, which was accompanied by non-histamine-dependent bronchospasm (69, 70). Ginkgolide B has been shown to be a potent inhibitor of PAF-induced thrombocytopenia and bronchoconstriction (71, 72). PAF or ovalbumin-induced bronchoconstriction in sensitized guinea-pigs was inhibited by an intravenous injection of ginkgolide B (1–3 mg/kg) 5 minutes prior to challenge (73).
Clinical pharmacology

Cerebral insufficiency

Cerebral insufficiency is an inexact term to describe a collection of symptoms associated with dementia (21, 22). In dementia owing to degeneration with neuronal loss and impaired neurotransmission, decline of intellectual function is associated with disturbances in the supply of oxygen and glucose. In clinical studies G. biloba effectively managed symptoms of cerebral insufficiency including difficulty in concentration and memory, absent-mindedness, confusion, lack of energy, tiredness, decreased physical performance, depressive mood, anxiety, dizziness, tinnitus, and headache (20–22). Several mechanisms of action of G. biloba have been described: effects on blood circulation such as the vasoregulating activity of arteries, capillaries, veins (increased blood flow); rheological effects (decreased viscosity, by PAF-receptor antagonism); metabolic changes such as increased tolerance to anoxia; beneficial influence on neurotransmitter disturbances; and prevention of damage to membranes by free radicals (22). Treatment of humans with G. biloba extract has been shown to improve global and local cerebral blood flow and microcirculation (74–76), to protect against hypoxia (77), to improve blood rheology, including inhibition of platelet aggregation (74, 78–81), to improve tissue metabolism (82), and to reduce capillary permeability (83).

A critical review of 40 published clinical trials (up to the end of 1990) using an orally administered G. biloba extract in the treatment of cerebral insufficiency concluded that only eight of the studies were well performed (21, 22). Almost all trials reported at least a partially positive response at dosages of 120–160mg a day (standardized extract) and treatment for at least 4–6 weeks (21, 22). In a comparison of G. biloba with published trials using co-dergocrine (dihydroergotoxine), a mixture of ergoloid mesilates used for the same purpose, both G. biloba extract and co-dergocrine showed similar efficacy. A direct comparison of 120mg of G. biloba standardized extract and 4.5mg co-dergocrine showed similar improvements in both groups after 6 weeks (84).

A meta-analysis of 11 placebo-controlled, randomized double-blind studies in elderly patients given G. biloba extract (150mg orally per day) for cerebral insufficiency concluded that eight studies were well performed (85). Significant differences were found for all analysed single symptoms, indicating the superiority of the drug in comparison with the placebo. Analysis of the total score of clinical symptoms indicated that seven studies confirmed the effectiveness of G. biloba extract, while one study was inconclusive (85).

Peripheral arterial occlusive disease

The effectiveness of G. biloba extract in the treatment of intermittent claudication (peripheral arterial occlusive disease Fontaine stage II), as compared with a placebo, was demonstrated in placebo-controlled, double-blind clinical trials by a statistically significant increase in walking distance (1, 23, 24). Sixty patients with peripheral arterial occlusive disease in Fontaine stage IIb
who were treated with the drug (120–160 mg for 24 weeks) and underwent physical training also clearly increased their walking distance (25).

Out of 15 controlled trials (up to the end of 1990) only two (23, 24) were of acceptable quality (22–24). The results of both studies were positive and showed an increase in walking distance in patients with intermittent claudication after 6 months (23), and an improvement of pain at rest in patients treated with 200 mg of G. biloba extract for 8 weeks (24).

After meta-analysis of five placebo-controlled clinical trials (up to the end of 1991) of G. biloba extract in patients with peripheral arterial disease, investigators concluded that the extract exerted a highly significant therapeutic effect (26).

**Vertigo and tinnitus**

Ginkgo biloba extracts have been used clinically in the treatment of inner ear disorders such as hearing loss, vertigo, and tinnitus. In a placebo-controlled, double-blind study of 68 patients with vertiginous syndrome of recent onset, treatment with G. biloba extract (120–160 mg daily, for 4–12 weeks) produced a statistically significant improvement as compared with the placebo group (27).

The results of clinical studies on the treatment of tinnitus have been contradictory. At least six clinical studies have assessed the effectiveness of G. biloba extract for the treatment of tinnitus. Three studies reported positive results (86, 87, 88). One multicentre, randomized, double-blind, 13-month study of 103 patients with tinnitus showed that all patients improved, irrespective of the prognostic factor, when treated with G. biloba extract (160 mg/day for 3 months) (86). Three other clinical trials reported negative outcomes (89–91). Statistical analysis of an open study (80 patients) without placebo, coupled with a double-blind, placebo-controlled part (21 patients), demonstrated that a concentrated G. biloba extract (29.2 mg/day for 2 weeks) had no effect on tinnitus (91).

**Contraindications**

Hypersensitivity to G. biloba preparations (20).

**Warnings**

No information available.

**Precautions**

*Carcinogenesis, mutagenesis, impairment of fertility*

Investigations with G. biloba extracts have shown no effects that were mutagenic, carcinogenic, or toxic to reproduction (20).
**Pregnancy: non-teratogenic effects**
The safety of Folium Ginkgo for use during pregnancy has not been established.

**Nursing mothers**
Excretion of Folium Ginkgo into breast milk and its effects on the newborn have not been established.

**Other precautions**
No information is available concerning general precautions or drug interactions, drug and laboratory test interactions, teratogenic effects on pregnancy, or paediatric use.

**Adverse reactions**
Headaches, gastrointestinal disturbances, and allergic skin reactions are possible adverse effects (20).

**Posology**
Dried extract (as described in Dosage forms), 120–240 mg daily in 2 or 3 divided doses (2); 40 mg extract is equivalent to 1.4–2.7 g leaves (20). Fluid extract (1:1), 0.5 ml 3 times a day (1, 2).

**References**
5. Farnsworth NR, ed. NAPRALERT database. 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).