

Ephedra

Species (Family)

Ephedra sinica Stapf., *E. equisetina*, *E. intermedia*, *E. geriardiana*, *E. major* and other *Ephedra* species that contain ephedrine (Ephedraceae)

Synonym(s)

Cao Ma Huang (Chinese Ephedra), Herba Ephedrae, Ma Huang. Ephedra (and some other herbs) has also been referred to as 'herbal ecstasy'.

Part(s) Used

Aerial parts

Pharmacopoeial and Other Monographs

Complete German Commission E^(G3)
Martindale 32nd edition^(G43)
PDR for Herbal Medicines 2nd edition^(G36)
WHO volume 1 1999^(G63)

Legal Category (Licensed Products)

Ephedra is not included in the GSL.^(G37)

Ephedra is included in Parts II and III of SI 2130.⁽¹⁾ This allows supply of ephedra (maximum dose of 600 mg and a maximum daily dose of 1800 mg) following a one-to-one consultation with a practitioner.

Ephedrine and pseudoephedrine are not included on the GSL. Both are prescription-only medicines (POM), but can be supplied through pharmacies at certain permitted doses, as follows. Ephedrine for internal preparations: maximum dose 30 mg, maximum daily dose 60 mg; nasal preparations, ephedrine 2%. Pseudoephedrine hydrochloride for internal preparations: maximum dose 60 mg, maximum daily dose 240 mg; prolonged-release preparations: maximum dose 120 mg, maximum daily dose 240 mg. Pseudoephedrine sulfate for internal preparations: maximum dose 60 mg, maximum daily dose 180 mg.

Constituents

Alkaloids 0.5–2.0%. Mainly (–)-ephedrine (30–90% in most species, except *E. intermedia*) and (+)-pseudoephedrine, also (–)-norephedrine, (+)-nor-

pseudoephedrine, (–)-methylephedrine and (+)-methylpseudoephedrine.^(2,G63)

Volatile oil Mainly terpenoids (e.g. α -terpineol, limonene, tetramethylpyrazine, terpinen-4-ol, linalol).⁽³⁾

Other constituents Tannins (catechin, gallic acid), ephedrans (glycans) and acids (citric, malic, oxalic).

Roots

Alkaloids Ephedroxane, ephedradines A to D, feruloylhistamine and maokonine.⁽⁴⁾

Flavonoids A flavonoflavonol (ephedrannin A), bisflavonols (mahuannins A to D).⁽⁴⁾

Food Use

Ephedra is not used in foods.

Herbal Use

Ephedra has traditionally been used for the treatment of bronchial asthma, hayfever, coughs and colds, fever, urticaria, enuresis, narcolepsy, myasthenia gravis, chronic postural hypotension and rheumatism.^(G32,G34,G36,G49,G54,G63,G64)

It is stated to have vasoconstricting, bronchodilating and central stimulating properties.^(G56) Modern interest in ephedra is focused on its use in cough and bronchitis,^(G56) and in nasal congestion due to hayfever, allergic rhinitis, common cold and sinusitis.^(G63) There is also interest in the potential of ephedra as an appetite suppressant.

Dosage

Herb 1.2–2.3 g cut herbs containing approximately 1.3% (13 mg/g) total alkaloids.^(G4)

Extract Adults: 15–30 mg alkaloids (maximum daily dose 300 mg), calculated as ephedrine.^(G56)

Tincture 6–8 mL (1 : 4) three times daily.^(G36)

In 1997, the US Food and Drugs Administration (FDA) proposed restrictions on the use of ephedra, although these restrictions have not, to date, been

implemented. The FDA proposals included a restriction on the maximum dose of ephedrine: 8 mg taken every 6 hours to a maximum daily dose of 24 mg for no more than seven days.^(5,G56)

Pharmacological Actions

The pharmacological properties of ephedra are due to the presence of ephedrine, pseudoephedrine and other ephedra alkaloids (see Constituents). Ephedrine and pseudoephedrine are sympathomimetic agents that have direct and indirect effects on both α - and β -adrenoceptors, as well as stimulating the central nervous system (CNS).^(G43,G63) Pseudoephedrine is stated to have less pressor activity and fewer CNS effects than ephedrine.^(G43)

In vitro and animal studies

Pharmacological activities documented for ephedrine and/or pseudoephedrine *in vitro* or *in vivo* (animals) include smooth muscle relaxant, cardiovascular, anti-inflammatory, immunomodulatory, CNS stimulatory and antimicrobial effects. The pharmacology of ephedra and its constituent alkaloids has been reviewed.^(4,6-8)

Ephedrine and pseudoephedrine have been stated to have a relaxant effect on bronchial smooth muscle in isolated rabbit lung and bronchi.⁽⁶⁾ Relaxant effects on gastrointestinal smooth muscle have also been noted.^(4,6)

Ephedrine has been shown to cause vasoconstriction and to have hypertensive effects in several animal models.^(4,6) Maakonine, a constituent of ephedra root, has been reported to be have hypertensive effects in anaesthetised rats.⁽⁹⁾ By contrast, other constituents of ephedra roots, such as ephedrannin A and feruloylhistamine, have been reported to have hypotensive activity.^(10,11) An aqueous extract of ephedra and its alkaloid fraction increased blood pressure, heart rate and blood glucose concentration in anaesthetised dogs following intravenous administration.⁽¹²⁾

Anti-inflammatory activity has been documented for ephedrine and pseudoephedrine in carrageenan-induced hind-paw oedema in mice.⁽¹³⁾ Oral administration of ephedrine and pseudoephedrine also inhibited hind-paw oedema induced by histamine, serotonin, bradykinin and prostaglandin E_1 . Crude extracts of ephedra have been reported to inhibit complement *in vitro*.⁽¹⁴⁾ Further investigation, using an aqueous extract of *E. sinica* leaves, showed that the complement-inhibiting component of ephedra inhibited the classical complement pathway in sera from several species, including human, pig, guinea-pig, rat and rabbit.⁽¹⁴⁾

In vitro antibacterial activity against several species, including *Staphylococcus aureus*, has been reported.⁽⁶⁾

In vitro studies have assessed the cytotoxicity of extracts of ephedra prepared under various conditions (e.g. using ground or unground material boiled for 0.5 or 2 hours) against a range of cell lines, including a human hepatoblastoma cell line (HepG2), a mouse neuroblastoma cell line (Neuro-2a) and a mouse fibroblastoma cell line.⁽¹⁵⁾ Ephedrine and ephedra extracts prepared from ground material appeared to be significantly more cytotoxic in these cell lines than did preparations from unground material. Also, Neuro-2a cells were more sensitive to ephedra extracts than were the other cell lines tested. Findings of this *in vitro* work also indicated that ephedra contains toxins other than ephedrine, as IC_{50} values were lower (i.e. indicating greater cytotoxicity) for ephedra extracts than for ephedrine alone.

Clinical studies

Pharmacokinetics Ephedrine and pseudoephedrine are readily absorbed from the gastrointestinal tract and are excreted, largely unchanged, in the urine.^(G43) Small amounts of metabolites following hepatic metabolism may be produced. The half-lives of ephedrine and pseudoephedrine range from 3 to 6 hours and from 5 to 8 hours, respectively, depending on urinary pH.^(G43)

In a study involving 12 healthy volunteers aged 23–40 years, four capsules of an ephedra product were administered twice, 9 hours apart. Each capsule contained ephedra 375 mg (*E. sinica*), with a mean (standard deviation (SD)) ephedrine content of 4.84 (0.45) mg.⁽¹⁶⁾ The half-life was reported to be 5.2 hours, maximum plasma concentration (C_{max}) was 81.0 ng/mL, the time to reach C_{max} (t_{max}) was 3.9 hours, and clearance was 24.3 L/hour.

In a randomised, crossover study, 10 healthy volunteers received ephedrine 25 mg or one of three ephedrine-containing nutritional supplements on one day during different phases of the study, each with a one-week washout period.⁽¹⁷⁾ Following single-dose administration of ephedrine 25 mg, mean (SD) half-life, C_{max} , t_{max} and clearance were found to be 5.37 (1.67) hours, 86.5 (15.4) ng/mL, 2.81 (1.35) hours and 28.5 (5.92) L/hour, respectively.

Therapeutic effects The pharmacological properties of ephedrine and pseudoephedrine in humans have been documented and include cardiovascular, bronchodilator and CNS stimulant effects.^(G43,G63)

Ephedrine is stated to raise blood pressure by increasing cardiac output and also by peripheral vasoconstriction. Ephedrine relaxes bronchial smooth muscle, reduces intestinal tone and motility, relaxes the bladder wall and reduces the activity of the uterus. Ephedrine is a CNS stimulant; this has led to its investigation for use in assisting weight loss.

A randomised, double-blind, placebo-controlled trial assessed the effects of a herbal combination preparation which included ephedra and other herbal ingredients.⁽¹⁸⁾ In the study, 67 overweight to obese individuals (body mass index 29–35 kg/m²) received the ephedra-containing preparation, or placebo, for eight weeks. Among the 48 participants who completed the study (24 in each group), a greater mean (SD) weight loss was noted for the treatment group, compared with the placebo group (4.0 (3.4) kg versus 0.8 (2.4) kg, respectively; $p < 0.006$).

Side-effects, Toxicity

The most common adverse effects of ephedrine and pseudoephedrine are tachycardia, anxiety, restlessness and insomnia.^(G43) Tremor, dry mouth, impaired circulation to the extremities, hypertension and cardiac arrhythmias may also occur with ephedrine, and skin rashes and urinary retention have been reported for pseudoephedrine.^(G43) There are isolated reports of hallucinations in children following use of pseudoephedrine.^(G43)

In the US, adverse effects have been reported following self-treatment with products containing ephedra alkaloids marketed for several uses, including as an aid to weight loss, to increase athletic performance, and as an alternative to illegal drugs of abuse.^(19,G43)

A review assessed 140 reports of adverse events related to the use of products containing ephedra alkaloids, usually combined with caffeine, submitted to the US FDA between June 1997 and March 1999.⁽¹⁹⁾ The main reasons for use of these products were weight loss (59%) and to increase athletic performance (16%); the reason for use was unknown in 17% of cases. Thirty-one per cent of cases ($n = 43$) were considered to be 'definitely' or 'probably' related to the use of products containing ephedra alkaloids, and a further 31% ($n = 44$) were judged to be 'possibly' related; for 29 cases, insufficient information was available to assess causation, and 24 cases were deemed to be 'unrelated' to use of these products. In several cases, individuals were thought to be ingesting up to 60 mg ephedra alkaloids daily. Of the 87 cases where causality was assessed, cardiovascular symptoms (mainly hypertension, palpitations, tachycardia) were the most com-

mon adverse events (47%). The most common CNS events were stroke ($n = 10$) and seizures ($n = 7$). Where events were 'definitely' or 'probably' related ($n = 43$), clinical outcomes were death (three cases), permanent impairment (seven) and ongoing treatment (four); a full recovery occurred in 29 cases.⁽¹⁹⁾

In a randomised, double-blind, placebo-controlled trial of a herbal supplement containing ephedra (72 mg/day) and guarana (240 mg/day), as well as other herbal ingredients, 23% ($n = 8$) of participants in the treatment group withdrew from the study because of adverse events (e.g. dry mouth, insomnia, headache) that may have been treatment-related; there were no withdrawals among placebo recipients.⁽¹⁸⁾

There are isolated reports of myocarditis,⁽²⁰⁾ exacerbation of autoimmune hepatitis,⁽²¹⁾ acute hepatitis,⁽²²⁾ nephrolithiasis⁽²³⁾ and psychiatric complications⁽²⁴⁾ associated with the use of ephedra-containing products. There is a report of sudden death associated with ephedrine toxicity in a 23-year-old man.⁽²⁵⁾ Several other reports also document psychosis and renal calculi following chronic use or misuse of ephedrine.^(G18)

In a study involving 12 normotensive adults who ingested four capsules each containing 375 mg powdered ephedra, followed by four more capsules nine hours later, a statistically significant increase in heart rate, compared with baseline values, was noted in six participants, although effects on blood pressure were variable.⁽¹⁶⁾

A study involving 47 dogs who were considered to have accidentally ingested herbal products containing ephedra and guarana reported that most dogs (80%) developed clinical signs of toxicosis, within eight hours of ingestion, which persisted for up to 48 hours.⁽²⁶⁾ Hyperactivity, tremors, seizures and behaviour changes were reported in 83% of dogs; other signs and symptoms included vomiting, tachycardia and hyperthermia.

Contra-indications, Warnings

Ephedra is stated to be contra-indicated in coronary thrombosis, diabetes, glaucoma, heart disease, hypertension, thyroid disease, phaeochromocytoma and enlarged prostate.^(G63) Another source states that ephedrine (and, therefore, ephedrine-containing products) should be used with caution in patients with diabetes, ischaemic heart disease, hypertension, hyperthyroidism, renal impairment and angle-closure glaucoma, and that in patients with prostate enlargement, ephedrine may increase difficulty with micturition.^(G43) It has been recommended to reduce the dose or discontinue treatment if nervousness, tremor,

sleeplessness, loss of appetite or nausea occur with use of ephedra preparations.^(G63)

Ephedrine-containing products should be avoided in patients receiving monoamine oxidase inhibitors as concomitant treatment may lead to a hypertensive crisis.^(G43) Ephedrine should also be avoided or used with caution in patients undergoing anaesthesia with cyclopropane, halothane or other volatile anaesthetics. There may be an increased risk of arrhythmias in patients receiving ephedrine together with cardiac glycosides, quinidine or tricyclic antidepressants, and there is an increased risk of vasoconstrictor or pressor effects in patients receiving ergot alkaloids or oxytocin.^(G43)

There is a report of a professional sportsman who tested positive for norpseudoephedrine after having consumed a liquid herbal product listing ephedra as one of the 15 ingredients.⁽²⁷⁾

Pregnancy and lactation There are no reliable data on the use of ephedra during pregnancy and lactation. The safety of ephedra during pregnancy and lactation has not been established and its use should be avoided.

Pharmaceutical Comment

The activities of ephedra are due to the presence of the ephedra alkaloids; of these, the pharmacological effects of ephedrine and pseudoephedrine are most well-documented and support their modern uses. There is less information on the pharmacological effects of ephedra extracts and clinical trials, in particular, are generally lacking.

In view of the safety concerns regarding the use of ephedra products, individuals wishing to use these products should be advised to consult an appropriately trained health care professional. Pharmacists and other health care professionals should be aware that ephedra may be included in unlicensed herbal products and food supplements under the name Ma Huang. Such products will not include reference to ephedra in the labelling.

References

See also General References G5, G18, G29, G31, G32, G34, G36, G43, G49, G54, G56, G63 and G64.

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