The Longwood Herbal Task Force
(http://www.mcp.edu/herbal/default.htm) and
The Center for Holistic Pediatric Education and Research
(http://www.childrenshospital.org/holistic/)

Ephedra (*Ephedra sinica*)

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Principal Proposed Uses: Decongestant, bronchodilator, CNS and cardiac stimulant, weight loss agent

Other Proposed Use: Diuretic

Overview

The major modern and historical uses for ephedra (also known as *Ma Huang*) are as a decongestant, bronchodilator, nervous and cardiovascular system stimulant, and weight loss remedy; traditionally it has also been used to treat dependent edema and water retention. Although there is long historical tradition to support the use of ephedra as a mild bronchodilator, more specific pharmacologic therapies have replaced it in mainstream medicine. It is effective as a decongestant, and it causes CNS and cardiovascular stimulation, accounting for many of its side effects. Data are mixed concerning its effectiveness as a weight loss agent, and there are substantial concerns about toxicity with both acute and chronic use. Ephedra can cause severe systemic reactions including tachyarrhythmias, hypertension, psychosis, collapse and even death when taken in high doses. No long term studies have evaluated ephedra's safety for chronic use. Typical doses used to treat allergic symptoms and asthma may lead to mild tachycardia, hypertension, insomnia, jitteriness and decreased appetite. The FDA has recommended a maximum of 8 mg up to every six hours (up to 24 mg daily) for up to seven days. Ephedra is not recommended for use during pregnancy, lactation or childhood.

Historical and Popular Uses

Ephedra altissima, a species closely related to modern *Ephedra sinica*, was found along with several other medicinal plants in a Neanderthal gravesite dating back 60,000 years[1]. Juice made from ephedra, known as "soma", was consumed as a longevity-producing beverage in ancient India. Ephedra has long been known and used as Ma Huang in Traditional Chinese Medicine (TCM) for over 5000 years[2]. Its historical uses include the alleviation of fevers, cough, colds, chills, shortness of breath, bone and joint pain, and water retention (edema). It was included in most TCM remedies for asthma[3].

Ephedra's primary chemical constituent, ephedrine, was isolated in 1887, and the isolated compound became popular in the US as a decongestant and bronchodilator during the 1920's. Even in the last quarter of the 20th century, ephedrine was used as a mainstream therapy for asthma and to correct hypotension resulting from spinal or epidural anesthesia even in laboring women[4]. Natural health enthusiasts have adopted ephedra as an herbal remedy for colds, asthma, allergic rhinitis, cough and bronchitis, and as an herbal weight loss agent[5]. It is also used as a CNS stimulant (to enhance alertness) and cardiovascular stimulant.

Ephedrine is also used as a starting material for the illegal manufacture of "speed" or methamphetamine[6]. Ephedrine itself is known as "natural ecstasy". Some athletes use ephedra to boost their performance naturally; however, in at least one case, an elite athlete was eliminated from competition because the product he used had been spiked with norpseudoephedrine, which is banned by the International Olympic Committee[7].

Due to over 800 reports of serious toxicity (including at least 22 deaths) among adolescents and young adults using ephedra as a natural stimulant[8], the US Food and Drug Administration (FDA) convened a special advisory committee on "Ephedra-containing Dietary Supplements." In June, 1997, the FDA adopted the policy that ephedra-containing products must 1) be labeled with all possible adverse effects, including death; 2) contain no more than 8 mg of ephedrine per serving; and 3) be used for no more than seven days[9]. The FDA also proposed a maximum daily dose of 24 mg and that combinations of ephedra and caffeine not be allowed to be marketed[10]. Several states, including Nebraska, Ohio and Texas, banned or severely limited

the sale of products containing ephedra in the late 1990's. However, products containing more than 10 mg of ephedra are available on line at several Web sites.

The German Commission E approves of the use of ephedra to treat "diseases of the respiratory tract with mild bronchospasm in adults and children over the age of six"; it also notes a variety of side effects and potential adverse interactions with commonly used medications[11].

Botany

Medicinal species: Ephedra sinica (Chinese ephedra)*, E. intermedia* (intermediate ephedra)*, E. equisetina* (Mongolian ephedra), and the North American species, *E. nevadensis.* There are approximately 40 species of Ephedra.

Common names: Cao mahuang (Ch), desert herb, ephedra, joint fir, Ma Huang, mahuang, "mao" (Ch), Mormon tea, popotillo, sea grape, squaw tea, teamster's tea, yellow horse, yellow astringent[12]

Botanical family: Ephedraceae

Plant description: Ephedra sinica is an erect, evergreen, shrub-like plant native to arid regions in China and Mongolia. Related species native to North America appear to be devoid of the active constituents. The parts used medicinally are the dried green stems. The plant has horse-shaped yellow flowers, accounting for one of its common names, "yellow horse". The plants have a strong pine-like odor and an astringent taste.

Where it's grown: Native to China, northern India, Pakistan and Mongolia[13, 14]. Now grown in arid regions around the world, including the southwestern US.

Biochemistry

Ephedra: Potentially Active Chemical Constituents
• Alkaloids: ephedrine, pseudoephedrine (isoephedrine), norpseudoephedrine (cathine), norephedrine, methylephedrine, methylpseudoephedrine[15]
• Tannins[16]
• Others, including quinoline and 6-hydroxykynurenic acid[17]

Ephedra's alkaloids, *ephedrine* and *pseudoephedrine*, are found in the leaves and stems, and are structurally related to amphetamines. They increase the availability and action of endogenous neurotransmitters, norepinephrine and epinephrine, and stimulate catecholamine receptors in the brain, heart and blood vessels both directly and indirectly.

The stem contains approximately 0.5-2.5% alkaloids, with ephedrine accounting for 30-90% of the total alkaloid content. The variation in content depends upon the species harvested and the part of the plant used; for example, the woody stems are low in alkaloids and the fruits and roots have practically none, while the softer stems contain up to 2.5% active alkaloids[12]. Plants grown in northern China have different morphology and alkaloid content from the same species grown in southern China[18, 19]. Different species, yielding markedly different quantities of active alkaloids, are all sold as Ma Huang in China, leading to tremendous difficulties for consumers trying to find standardized products[20]. *E. sinica* generally contains substantially greater concentrations of alkaloids than *E. intermedia*[21, 22]. The North American species, *E. nevadensis* (Mormon tea, Mexican tea, squaw tea or desert tea), is apparently devoid of alkaloids altogether[23]. Different extraction methods also yield different quantities of active compounds[24].

Ephedrine is well absorbed after oral administration; it has a half life of three to six hours. Following oral administration, 88% is excreted in the urine within 24 hours, and 97% is excreted within 48 hours. In the plant, pseudoephedrine is typically dextro-rotatory (D-pseudoephedrine), and ephedrine is typically levorotatory (L-ephedrine), while synthetically manufactured ephedrine is usually a racemic mixture of both forms. The natural and synthetic forms have very similar absorption and pharmacokinetics in adults, but the available natural products contain considerably different concentrations of active alkaloids; pharmacokinetics have not been formally studied in children[25, 26].

Both ephedrine and pseudoephedrine have well described physiologic effects including central nervous system stimulation, bronchodilation, hypertension, and both chronotropic and inotropic effects[27]. The synthetic form of pseudoephedrine is widely used in non-prescription decongestants. Orally administered ephedra can cause CNS symptoms such as dizziness, restlessness, irritability, insomnia, headache and anorexia. Ephedrine can also cause uterine stimulation and has diuretic effects. It crosses the placenta and increases fetal heart rate[4, 28]; it

also crosses into breast milk and can cause irritability, crying and insomnia in the infant[29]. Pseudoephedrine is a more potent diuretic than ephedrine.

Tannins have astringent effects and are often used in topical preparations to reduce oozing and weeping in skin lesions. Ephedra's tannins are thought to provide some renal protection, at least in experimental models of renal failure in rats[30].

Experimental Studies

Ephedra: Potential Clinical Benefits
1. Cardiovascular: Chronotropic, anti-hypotensive
2. Pulmonary: Bronchodilator, decongestant
3. Renal and electrolyte balance: Diuretic
4. Gastrointestinal/hepatic: none
5. Neuropsychiatric: none
6. Endocrine: Enhanced thermogenesis and weight loss
7. Hematologic: none
8. Rheumatologic: none
9. Reproductive: Uterotonic
10. Immune modulation: Anti-inflammatory
11. Antimicrobial: none
12. Antineoplastic: none
13. Antioxidant: none
14. Skin and mucus membranes: none
15. Other/miscellaneous: Potential for abuse as a natural stimulant

1. **Cardiovascular**: Chronotropic, anti-hypotensive. A substantial body of historical and clinical experience supports the potent cardiovascular stimulant effects of ephedrine and related sympathomimetic compounds.
   a. Chronotropic (increases heart rate). Tachycardia is a frequently reported side effect of ephedrine use[31]. However, no studies have formally compared the tachycardic effects

induced by ephedra with those from other chronotropic agents. (See **Toxicity and Contraindications** section below.)

b. Anti-hypotensive

i. *In vitro data:* none

ii. *Animal data:* Although ephedrine is well known to increase blood pressure, the *roots* of the plant (known as *Mao Kon* in TCM) exert hypotensive effects in rats when given in doses of 0.1-0.3 mg/kg intravenously[32].

iii. *Human data:* In a series of 12 normotensive adults given an ephedra product in the morning (approximately 20 mg ephedrine and 5 mg pseudoephedrine per dose) and another dose nine hours later, no adverse effects on blood pressure were found, although 50% had significant tachycardia[31].

Ephedrine has been used to combat the hypotensive effects of epidural and spinal anesthesia during labor and delivery[4, 28].

2. **Pulmonary**: Bronchodilator, decongestant

a. Bronchodilator: Ephedra has long been used as a bronchodilator to treat asthma and chronic obstructive pulmonary disease. The use of ephedrine to treat asthma in children was first reported in western medicine in 1927[33]; its clinical effectiveness and side effects, including the death of a child from an accidental overdose of an ephedra-containing asthma medication, were subsequently reported in several studies[34-38]. The synthetic forms of ephedrine were used to treat asthma until the advent of more specific beta agonist medications.

i. *In vitro data:* none

ii. *Animal data:* none

iii. *Human data:* In a double-blind, placebo controlled study of 16 asthmatic children (13 of whom were being treated with aminophylline and four of whom were receiving alternate day prednisone co-therapies), ephedrine sulfate (25 mg every eight hours) led to a significant improvement in pulmonary function tests within 30 minutes of administration; benefits lasted three to four hours[39].

b. Decongestant: Although ephedra has a long history of use as a decongestant, and the synthetic form of pseudoephedrine is widely used as decongestant medication, the crude

herbal products have not been evaluated in direct comparison with decongestant medications.

3. **Renal and electrolyte balance:** Diuretic. Ephedra is used as a diuretic in TCM; the North American species, *E. nevadensis*, was used by Native Americans for the same purpose[23, 40]. However, there are no recent studies evaluating the effectiveness of *E. sinica* as a diuretic either in animals or humans, and none comparing it with known diuretic medications.
4. **Gastrointestinal/hepatic:** none
5. **Neuropsychiatric:** none
6. **Endocrine:** Enhanced thermogenesis and weight loss
   i. *In vitro data:* Ephedrine stimulates thermogenesis in adipocytes *in vitro* and in animal studies; this effect appears to be enhanced with chronic administration[41].
   ii. *Animal data:* In mice, rats and monkeys, ephedrine led to significant weight loss, primarily by enhancing thermogenesis and secondarily through anorexia[42-46]; this effect was enhanced by combining ephedrine with aspirin and/or methylxanthines (caffeine or theophylline), even in animals genetically predisposed to extreme obesity[47-51].
   iii. *Human data:* Case reports and randomized trials suggest that ephedra may be a useful addition to a comprehensive weight loss program. However, some studies have had high drop out rates, significant side effects in the first month of treatment, and only marginal improvements in weight loss.

      Among five obese women, the effects of one acute dose of ephedrine (1 mg/kg) were assessed and compared with long-term ephedrine treatment (20 mg three times daily). Acute administration led to significant increases in resting blood pressure, while chronic administration led to significant weight loss (5.5 kg over three months, $P<0.01$), increased plasma glucose and noradrenaline concentrations, and increased oxygen consumption, reflecting enhanced thermogenesis[52].

      In a placebo controlled trial, 46 obese adults were treated with a low calorie diet and either 75 or 150 mg daily of ephedrine or placebo for three months; body mass index (BMI) fell significantly in a dose dependent fashion with ephedrine treatment. Side effects such as agitation, palpitations and tremor were more common with the higher dose of active drug, but tended to subside within the first two months of treatment[53].

Similarly, in a group of ten obese women whose weight had remained stable even on a low calorie diet, ephedrine (50 mg three times daily) was significantly more effective than placebo in reducing BMI over one month[53]. Furthermore, in a double-blind randomized, controlled cross-over study of obese women who were on a low calorie diet (1000-1400 calories daily), treatment with ephedrine supplements (50 mg three times daily for two months) resulted in significantly greater weight loss than placebo treatment (2.4 vs. 0.6 kg weight loss, $P<0.05$); side effects included mild agitation (2/10 patients), insomnia (3/10 patients), palpitations (2/10 patients) and giddiness (2/10 patients)[54].

Less promising results were reported in a double-blind, controlled trial among 62 obese adults who were on a low calorie diet (1000 calories daily for women; 1500 calories daily for men). One group was assigned to high dose ephedrine (50 mg three times daily), one group to low dose ephedrine (25 mg three times daily) and one group to placebo for three months. Among the 46 patients who completed at least one month of treatment, there was no significant improvement in BMI with ephedrine treatment; the high rate of dose-related side effects led to a substantial drop out rate, especially during the first month of the study[55].

Combining ephedrine with caffeine and other methylxanthines appears to offer somewhat greater benefits in terms of thermogenesis and weight loss. In a randomized, placebo controlled, double-blind study, 180 obese adults were treated with a low calorie diet and either an ephedrine/caffeine combination (20mg/200mg), ephedrine alone (20 mg), caffeine alone (200 mg) or placebo three times a day for 24 weeks. Mean weight loss was significantly greater with the ephedrine/caffeine combination than with placebo or either individual agent ($P < 0.01$)[56, 57]. In a double-blind, randomized, placebo controlled trial with an identical treatment regimen, weight loss was significantly better with either the ephedrine alone or the ephedrine/caffeine combination than with placebo or caffeine alone; the weight loss was maintained and improved over an additional 24 weeks of open-label treatment[58]. In another randomized, double-blind, placebo controlled trial, 24 obese adults (mean BMI =37) were given either placebo or a combination of ephedrine (75-150 mg), caffeine (150 mg) and aspirin (330 mg) before

meals daily for eight weeks; overall weight loss was significantly greater for the active treatment group (2.2 vs. 0.7 kg, $P<0.05$) even without caloric restrictions[59].

On the other hand, in a randomized, controlled trial, 22 obese women received a low calorie diet and either placebo, ephedrine (50 mg three times daily) or a combination of ephedrine and caffeine (50 mg/100 mg three times daily) for four months; weight loss was 7-10 kg on average and did not differ significantly between groups[53].

Recent reviews conclude that the weight loss effects of ephedrine are mild or modest at best, and newer agents appear to offer greater benefits[60]; however, ephedrine is still under active investigation and professional opinion on its role in weight loss programs is divided. There are substantial concerns about safety and toxicity, particularly for combining ephedra with methylxanthines (See **Toxicity and Contraindications** section below.)

7. **Hematologic:** none
8. **Rheumatologic:** none
9. **Reproductive:** Uterotonic. Historically, ephedra has not been recommended during pregnancy because it was thought to have uterotonic effects. We were unable to find recent studies evaluating its effects on uterine tone or contractions.
10. **Immune modulation:** Anti-inflammatory. In TCM, ephedra is used to treat asthma and acute nephritis. It is typically used in conjunction with other anti-inflammatory herbs such as licorice.
    i. *In vitro data:* Ephedra extracts inhibit complement activity *in vitro*[61].
    ii. *Animal data:* Ephedra's stems demonstrated anti-inflammatory activity in the mouse paw model of carageenan-induced inflammation[62]. Its anti-inflammatory effects are thought to be due to the pseudoephedrine content[63].
    iii. *Human data:* none
11. **Antimicrobial:** none
12. **Antineoplastic:** none
13. **Antioxidant:** none
14. **Skin and mucus membranes:** none
15. **Other/miscellaneous**: Potential for abuse as a natural stimulant

Toxicity and Contraindications

All herbal products carry the potential for contamination with other herbal products, pesticides, herbicides, heavy metals, and pharmaceuticals. This is particularly concerning for imports from developing countries.

Furthermore, allergic reactions can occur to any natural product in sensitive persons.

Allergic reactions and contact dermatitis to ephedra have been reported.

Potentially toxic compounds in ephedra: Ephedrine and pseudoephedrine

Acute toxicity: Ephedrine can lead to anxiety, dizziness, jitteriness, insomnia, chest tightness, decreased appetite, hypertension, tachycardia, arrhythmias, stroke, urinary retention, vomiting, psychosis, and even death[64-69]. Ephedrine has been used to commit suicide[70, 71]. Case reports have cited other side effects including myalgia, cardiomyopathies, rhabdomyolysis, nephrolithiasis, acute hepatitis, eosinophilia-myalgia syndrome, Parkinsonism, and acute myocarditis[73-76]. Crude extracts of a related species, *E. distachya*, have also resulted in hypoglycemia in normal and diabetic mice[72].

Chronic toxicity: Ephedrine can lead to weight loss, insomnia and other amphetamine-like side effects, including hypertension, dry mouth, arrhythmias, palpitations, anxiety and nervousness. Sustained use may lead to cardiac hypertrophy and focal myocardial necrosis[77, 78]. Tea made from the European species, *E. altissima*, exhibited mutagenic effects in the standard Ames test for mutagenicity[79, 80].

Limitations during other illnesses or in patients with specific organ dysfunction: Patients with hypertension, angina and other heart problems, cerebral insufficiency, diabetes, depression, glaucoma, thyroid disease, anxiety disorders, insomnia, anorexia/bulemia, tremor, kidney stones, urinary retention, or benign prostatic hypertrophy should use extreme caution when considering the use of ephedra[74, 81, 82].

Interactions with other herbs or pharmaceuticals: Ephedra should be used only with great caution by patients taking MAO-inhibiting antidepressants, CNS or cardiovascular stimulants, or decongestants because of the risk of severe hypertension[11]. Combining ephedra with methylxanthines such as caffeine may increase the risk of adverse effects[83].

Ephedrine may increase steroid clearance, reducing the effectiveness of dexamethasone; it could also interfere with antidiabetic drugs by increasing blood sugar levels[82]. Ephedra could theoretically increase the risk of cardiac arrhythmias in patients taking digoxin, other cardiac glycosides or halothane; it could enhance the hypertensive effects of ergotamine[11].

Safety during pregnancy, lactation and/or childhood: Ephedrine crosses the placenta and into breast milk and can adversely affect fetuses and infants; it may also cause uterine stimulation[4]. Ephedrine should not be used during pregnancy, lactation or by children less than 18 years old[82].

Typical Dosages

Provision of dosage information does NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used in herbal practice.

Doses are given for single herb use and must be adjusted when using herbs in combinations.

Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Adult doses: There is disagreement on the optimal form and dose of ephedra. The FDA recommends restricting doses to less than 24 mg ephedrine daily. If the average ephedra content is 1% of the crude plant, and the maximum daily dose of ephedrine recommended by the US FDA is 24 milligrams, this would translate into 2400 mg daily (800 mg TID) of the raw herb. Traditionally, herbalists have recommended a wide range of doses which are typically higher than the FDA recommendations. Doses up to 25 mg of total ephedra alkaloids up to four times daily have been recommended by some experts, and doses in some studies have been 50-100 mg of ephedra three times daily.

Crude drug (herb): 1-4 grams daily, steeped in 150 ml boiling water and divided into 4-6 doses

Tinctures: (1:1) 1-4 ml three times daily

(1:4) 6-8 ml three times daily

Fluid extract: 1-3 ml three times daily

Typical doses of *pseudoephedrine* are 60 mg every four to 12 hours.

Availability of standardized preparations: None

Dosages used in herbal combinations: Variable

Pediatric dosages: Unknown

Multi-ingredient preparations containing ephedra: Acceleration, AllerClear, AllerPlus, Andro Heat, Better BodyEnergy for Life, Bio Trim, Biovital Plus, Bladderwrack-Dandelion Virtue, Breathe-Aid Formula, Breath Easy, Cordephrine XC, Diet Fuel, Dymetadrine Xtrem, EPH-833, Ephedra Plus, Thermogen, Guarana-Gotu Kola Virtue, Herba Fuel, Herbal Decongestant Expectorant Capsules, Herbalife - Thermojetics Original Green, Metabolife 356, Metabolift, Metaboloss, MetaboTRIM, Naturafed, Naturally Ripped,

Naturatussin 1, Nettle-Reishi Virtue, Power Thin, ProLab Stoked, Pro-Ripped Ephedra, Respa-Herb, Respiratory Support Formula, Ripped Fuel, SinuCheck, SinuClear, SnoreStop, Thermadrene, Thermic Blast, Thermicore, Thermo Cuts, ThermoDiet, Ultra Diet Pep, Xenadrine RFA-1

See Also:

Ephedra Clinician Information Summary: http://www.mcp.edu/herbal/ephedra/ephedra.cis.pdf

Ephedra Patient Fact Sheet: http://www.mcp.edu/herbal/ephedra/ephedra.ph.pdf

Naturaldatabase.com: http://www.naturaldatabase.com (available by subscription only)

Drugstore.com: http://www.drugstore.com/guide/Herb/Ephedra.asp

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