

# Ma Huang (Ephedra)

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## Ephedra botanical

The Chinese herb Ma Huang has been used for over 5000 years as a circulatory stimulant, diaphoretic, antipyretic and a cough suppressant. Ma Huang is prepared from a desert dwelling shrub in the Ephedra genus. Over 50 species of Ephedra exist throughout the world. Three Asian species of Ephedra, *Ephedra sinica*, *E. intermedia*, and *E. equisetina*, are commonly used for medicinal purposes. The active component in Ephedra, called ephedrine, was isolated by Japanese researchers Yamanashi, Hori and Nagai in 1887. In 1927, ephedrine was chemically synthesized and shortly thereafter was approved for use by American Medical Association as a sympathomimetic drug with relatively low toxicity compared to epinephrine (reviewed by Chen, 1930).

## Ephedrine structure and derivatives

Ephedrine is a benzyl alkaloid (nitrogen containing organic molecule) that resembles natural and synthetic stimulants such as epinephrine and methamphetamine (Figure 1). The alkaloid content of Ephedra differs in specific species. For example the American species *Ephedra Novadensis* (Mormon tea) is reported to have little or no ephedrine alkaloid. On the other hand, the stems and branches of *Ephedra sinica* contains 1-3% alkaloids, of which 40-90% is ephedrine. Ma Huang is known to contain at least 6 different ephedrine-type alkaloids including (-)-ephedrine, (-)-norephedrine (demethylated ephedrine), (-) N-methylphedrine and their stereoisomer (+)-pseudoephedrine, (+)-norpseudoephedrine and (+)-N-methyl pseudoephedrine.

## Use of Ma Huang in Traditional Chinese Medicine

Historically Ma Huang was used in Chinese medicine to treat common cold, asthma, hay fever, bronchitis, edema, arthritis, fever and hypotension (Pizzorno and Murray, 1999). Today it is used as a bronchodilator to treat mild asthma and hay fever. The therapeutic effect of Ma Huang diminishes with time and is thought to weaken the adrenal gland. Therefore, Ma Huang is often given in combination of with herbs and nutrients to support the adrenal glands. In some cases Ma Huang is given in combination with herbal expectorants to treat symptoms associated with influenza, pneumonia, whooping cough and bronchitis. Depending on the species of Ephedra used in the preparation, a crude extract of 0.5-1.0 grams (equivalent to 12.5-25 mg ephedrine) is administered two to three times daily for a period of 5-7 days.

Long-term use of Ma Huang is not common practice in TCM.

## Pharmacology

Alkaloids are nitrogenous compounds that often contain one or more phenolic or indole rings. The position of the nitrogen atom(s) varies from within the carbon ring to different positions in the alkyl side chain. The precise position of the nitrogen atom and the length and constituents of the side chain affect the properties of these alkaloids.

Alkaloids such as ephedrine and epinephrine are powerful cardiovascular and central nervous system stimulants.

Ephedrine functions, similarly to epinephrine, by stimulating the alpha and beta-adrenergic receptors which results in an increase in both systolic and dias-

tolic blood pressure, an increase in circulation, and bronchodilator. In general, the effect of ephedrine on the cardiovascular system is less potent than that of epinephrine, but is longer lasting (up to 10 times longer). Unlike epinephrine however, ephedrine also has a pronounced stimulatory effect on the central nervous system. This effect of ephedrine is similar to that produced by the structurally similar amphetamine. Again, the CNS effect of ephedrine is less potent but longer lasting than that which is produced by amphetamine.

Another alkaloid found in Ephedra is pseudoephedrine. The effect of pseudoephedrine is similar to ephedrine for bronchodilator. However, pseudoephedrine has less of an effect on the cardiovascular system than ephedrine. Synthetic drugs containing pseudoephedrine are common and now marketed as effective and safe bronchodilators in over-the-counter drugs such as Sudafed®.

Racemic norephedrine (phenylpropanolamine, PPA) – was taken of the market as an appetite suppressant after reports that it significantly increased the risk of stroke in 1 in 100,000 women. (Kernan et al., 2000)

Norpseudoephedrine is classified as a Schedule IV controlled substance.

## Toxicity and adverse effects associated with Ephedrine

Controlled randomized clinical trials that address the specific risks of ephedrine or Ma Huang alone in normal individuals are lacking. However, because of the established sympathomimetic effects of ephedrine, Ephedra herbal products pose a potential risk of life-threatening adverse effects. Thus, based on FDA guidelines on the use of ephedrine, the use of Ma Huang containing supplements should be avoided in pregnant women and individuals with heart disease, high blood pressure, thyroid disease, diabetes or an enlarged prostate gland.

Recent studies indicate significant temporal association between the use of

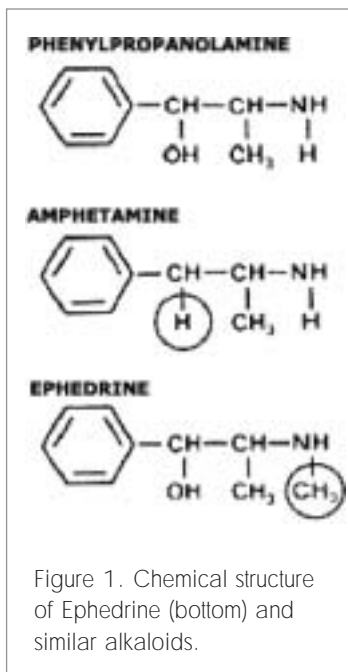


Figure 1. Chemical structure of Ephedrine (bottom) and similar alkaloids.

ephedrine containing supplements and risk of adverse effects on cardiovascular and central nervous systems (Haller et al., 2000; Samenuk et al., 2002). However, it is important to note that these studies contain significant omission of relevant information about the cases that weaken the relationship between the consumption of the supplements and adverse effects. For example, a review of 22 deaths associated with Ephedra in Adverse Event Report (AERs) collected by FDA, 20 deaths could be attributed to causes other than ephedrine such as congenital heart disease, coronary artery disease, myocarditis or extreme fasting or exercise (Hutchins, 2002). Moreover, little information was given regarding whether these effects were associated with Ephedra alone or when Ephedra was used in combination with other stimulants in these cases.

## Variation within and among Ephedra preparations

- Betz et al. (1997) – 0.3-56 mg/g variability in the amount of alkaloids in products.
- Gurley et al. (2000) variation even within products.

## FDA ruling

The Dietary Supplement Health and Education Act (DSHEA) was passed by the FDA in 1994, stipulating that “dietary supplements” are exempt from the same rigorous regulation of prescription drugs or non-prescription drugs. In order for the FDA to impose regulations on any supplements, DSHEA places the burden of proof on the government to show “significant or unreasonable risk of illness or injury” under conditions suggested by the product labeling or under ordinary conditions of use if the labeling is silent. Unreasonable risk is determined if the risk outweighs the benefits associated with the supplement. At present, the evidence for the long-term benefit of Ephedra containing dietary supplements for weight loss or enhancing athletic performance is weak and requires a large scale controlled clinical trial to be accurately determined. However, on February 4th, 2004 the Department of Health and Human Services and FDA issued a final regulation declaring dietary supplements containing ephedrine alkaloids adulter-

ated under the Food, Drug and Cosmetic Act. As a consequence these products can no longer be sold in the United States. This regulation states in its preamble that “This final rule does not affect the use of Ephedra preparations in traditional Asian medicine,” or change how such products are regulated. The FDA’s view is that “Traditional Asian medicine practitioners do not typically use products marketed as dietary supplements.” Despite this ruling, vendors of Traditional Asian Medical products continue to have difficulty with the importation of their products at the American border.

## Rand report

According to the FDA report Feb. 28, 2003, the study by Shekelle et al., (2003) by the RAND corporation represents the “best compilation of evidence yet on the safety of Ephedra.” The RAND report includes a thorough review of 52 controlled clinical trials of ephedrine or herbal Ephedra for weight loss or athletic performance in humans in addition to over 16,000 case reports including AERs related to ephedrine or Ephedra herbal products. These studies concluded that Ephedra supplements had a small but significant short-term benefit on weight loss and no significant benefit on athletic performance. Importantly, no studies addressed the long-term benefit of Ephedra supplements on weight loss. The data obtained from the combination of all of the clinical trial available to date are not sufficient to determine serious adverse events that would occur at a frequency of less than 0.1%. The study also found that the majority of the case reports were insufficiently documented to allow a determination of a relationship between the use of ephedrine containing supplements and adverse events. However, they reported 22 “sentinel” events including 2 deaths, 3 myocardial infarctions, 9 cerebrovascular accidents, 3 seizures, and 5 psychiatric cases. However, it is possible that the incidence of these events in this study may only reflect the normal frequency of occurrence of these events in the general population in the United States.

## Conclusions

Ephedrine containing herbs have been used for thousands of years to effectively and safely treat asthma, congestion, and

bronchial dilation by oriental medicine practitioners. However, the recent use of ephedrine-containing products with other stimulants such as caffeine and Aspirin to enhance athletic performance or promote weight loss has lead to a rapid rise in the incidence of adverse events. As a result, the Department of Health and Human Services and the FDA issued a final regulation declaring dietary supplements containing ephedrine alkaloids as ‘adulterated’ under the Food, Drug and Cosmetic Act. Despite a FDA exemption that allows for traditional use of ephedra by practitioners of Asian Medicine, issues of successful importation have arisen at the American border.

However, the FDA is making attempts to communicate with and to cooperate with practitioners and importers of Traditional Asian herbal products in order to answer questions and find solutions to problems that importers are having with delayed herbal shipments. Currently the AAOM is having ongoing discussions with the FDA.

(Gurley et al. 2000; Haller et al. 2000; Kernan et al. 2000; Hutchins 2001; Hutchins 2002; Samenuk et al. 2002)

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## References

- Chen, 1930
- Pizzorno and Murray, 1999
- Gurley, B. J., et al. (2000). Content versus label claims in Ephedra-containing dietary supplements. *Am J Health Syst Pharm* 57(10): 963-9.
- Haller, C. A., et al. (2000). Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 343(25): 1833-8.
- Hutchins, G. M. (2001). Dietary supplements containing ephedra alkaloids. *N Engl J Med* 344(14): 1095-6; author reply 1096-7.
- Hutchins, G. M. (2002). Ma huang toxicity. *Mayo Clin Proc* 77(7): 733.
- Kernan, W. N., et al. (2000). Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 343(25): 1826-32.
- Samenuk, D., et al. (2002). Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc* 77(1): 12-6.
- Shekelle P, Morton, S., Maglione M, et al. Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects. Evidence Report/Technology Assessment No. 76 (Prepared by Southern California Evidence-based Practice Center, RAND, under Contract No 290-97-0001, Task Order No. 9). AHRQ Publication No. 03-E022. Rockville, MD: Agency for Healthcare Research and Quality. February 2003.