

Review

A deficiency of Yang by overuse of Ephedra in traditional medicinal aspects

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ABSTRACT

Ephedra and ephedra alkaloids are sympathomimetic compounds extracted from the genus Ephedra. They have been used to treat colds and provide cough relief for centuries in oriental medicine. Recently, it has been reported that Ephedra plays a crucial role in weight loss and the enhancement of athletic performances. However, the overuse of Ephedra causes cardiovascular side effects such as increases in blood pressure, heart rate, and palpitations. Ephedra's adverse effects also were mentioned in Shan Han Lun, a famous formulary in traditional Chinese medicine. The present study demonstrated Ephedra's effects and the deficiency of Yang due to the overuse of Ephedra.

Keywords Ephedra, Yang, side effects

INTRODUCTION

Ephedra or the Ephedra alkaloid is a group of sympathomimetic compounds extracted from the genus Ephedra. There are around 40 species throughout the temperate and subtropical regions of Asia, Europe, and the Americas. The Asian species, including *E. sinica*, *E. intermedia*, and *E. equisetina*, have the highest alkaloid content (Tang, 1996). Ephedra alkaloids have been used for centuries as a traditional remedy, particularly among the people of East Asia. The principle alkaloid, *ephedrine*, was first isolated in 1885 and has found use in its purest form in modern medicines, including as a bronchodilator, decongestant, and vasopressor (USPDI, 1999). In recent years, various companies have begun the use of extracts of Ephedra shrubs for purposes such as weight loss and the enhancement of athletic performances. Herbalists also use them as "alternative medicines" for colds and cough relief. It has been estimated that nearly one third of young, obese women have used a weight-loss supplement containing Ephedra (Blank et al., 2001). In 1999 alone, 12 million individuals in the United States used 3 billion doses of Ephedra alkaloids (Haller and Benowitz, 2000). Given the frequency of reports of adverse cardiovascular and cerebrovascular complications, the U.S. Food and Drug Administration (FDA) recently moved to prohibit the sale of these supplements.

In oriental medicine, there have been a number of reports about Ephedra's adverse complications and treatment methods. Specially, in Shan han lun (傷寒論), overusing Ephedra is regarded as a deficiency of Yang (陽) and some remedies are used to treat this situation. The present review demonstrates Ephedra's effects and the deficiency of Yang (陽)

EPHEDRA**Structure and pharmacology**

Ephedra is a generic term for several sympathomimetic agents including ephedrine, pseudoephedrine, norpseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, and phenylpropanolamine (a synthetic, racemic mixture of the stereoisomers of norephedrine). They are closely related, substituted molecules that demonstrate significant similarities with amphetamines and other catecholamines. These molecules possess significant α - and β -adrenergic agonist activities. In addition, they enhance the release of endogenous catecholamines. This latter effect, through the depletion of endogenous catecholamine stores, is thought to explain the tachyphylaxis noted with repeated dosing (Haller and Benowitz, 2000). The principle cardiovascular effects of Ephedra alkaloids include increases in systolic and diastolic blood pressure, heart rate and indices of cardiac performance (USPDI, 1999; Waluga et al., 1999).

In the species of Ephedra that contain appreciable quantities of the alkaloids, the greatest amount is found in the branches, whereas the remainder of the shrub is devoid of the compounds. The dried branches of the Asian species are known as *ma huang* in Chinese, meaning "yellow astringent". Extracts of the branches contain varying amounts of different alkaloids and each alkaloid differs somewhat in its pharmacodynamic properties. From 40% to 90% of the alkaloid content consists of ephedrine with other agents comprising the remainder in relatively smaller quantities by Cantox report (Cantox Health Sciences International, 2000).

The absorption of ephedrine from the gastrointestinal tract is very efficient, approximately 100% (Cantox Health Sciences International, 2000). The pure alkaloid is absorbed most quickly. Herbal alkaloid mixtures may retard the rate of absorption; however, the rate of absorption of ephedrine may be increased with heat stress (Vanakoski et al., 1993). Additionally, elevations in blood pressure are significantly greater when ephedrine is taken during heat stress. The importance of this finding lays in the fact that Ephedra extracts have been marketed as enhancers of athletic performance and have been often taken prior to exercise in a warm environment.

Thus, they may add to the cardiovascular stress already being experienced during physical activity. Once absorbed,

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ephedrine has a large volume of distribution and is not bound to plasma proteins (Cantox Health Sciences International, 2000). Ephedrine and the related alkaloids are lipophilic and cross the blood-brain barrier. Therefore, the compounds are closely related with their effects on the central nervous system, which include appetite suppression, anxiety, and gastric motility changes (Astrup et al., 1998; Astrup et al., 1995; Bray 1999; Breum et al., 1994; Jonderko and Kucio, 1991; Shekelle et al., 2003a). The effects of ephedrine last for approximately 1 h (USPDI, 1999), whereas the serum half-life ranges from 3 to 11 h (Cantox Health Sciences International, 2000). Excretion occurs primarily through the kidneys over 24 h, predominately in the unchanged form. From 8% to 20% is excreted after demethylation and delamination (Cantox Health Sciences International, 2000). Excretion is pH dependent because of an ionizable amino group in the molecule. Acidic urine promotes excretion because the amino group is then positively charged and not readily reabsorbed; alkaline urine has the opposite effect (Haller et al., 2002; Lyons and Turnay, 1996). In addition to renal excretion, ephedrine is also found to be excreted in breast milk and crosses the placenta, which poses concerns for fertile women who may be using extracts for weight loss purposes while pregnant or after delivery.

Effects on weight loss and athletic performance

Several studies on these compounds (particularly ephedrine) have been undertaken to assess their efficacy and safety in humans for the treatment of obesity (Astrup et al., 1992a, 1992b; Boozer et al., 2002; Breum et al., 1994; Daly et al., 1993; Dulloo, 2002; Greenway, 2001; Greenway et al., 1999; Pasquali et al., 1985; Toubro et al., 1993). In these trials, doses of ephedrine and related compounds ranged from 60 to 150 mg/d, and overall, the studies have shown statistically significant reductions in the weight of obese patients treated with Ephedra alkaloids versus those treated with a placebo. These findings were corroborated by Rand Report (Shekelle et al., 2003b). However, in their results, they showed that the experimental group experienced a modest incidence of cardiovascular side effects, even when they were treated the compounds with carefully controlled doses. These side effects included increases in blood pressure (both systolic and diastolic), heart rate, and palpitations that were often mild and transient.

Adverse effects

People pay much attention to the adverse effects related to the use of Ephedra alkaloids, such as toxicity, blood pressure and myocardial ischemia. Even though much research showed the safety of Ephedra alkaloids, they are still difficult to extrapolate to the usage of the supplements because the study materials are often pure, minor constituents (such as pseudoephedrine), which are used under controlled conditions (Porta et al., 1986). Insight into the potential toxicity of these agents may be obtained by considering their pharmacologic properties. Ephedra alkaloids are α - and β -adrenergic agonists that stimulate the release of endogenous catecholamines. Even with these new studies, the physiological effects of the compounds with these properties have been known for decades, (Andraws et al., 2005).

In addition to effects on blood pressure and cardiac performance, the compounds cause vasoconstriction and vasospasm, including coronary vasospasm (Zahn et al., 1999). Moreover, there is some evidence that, along with spasms, Ephedra alkaloids may induce hypercoagulable states, imbalance within the coronary circulation. This could account for reported cases of myocardial infarction in otherwise healthy young people without a significant underlying coronary artery

disease (Cockings and Brown, 1997; Derreza et al., 1997; Pederson et al., 2001; Wiener et al., 1990). Myocardial ischemia has also been reported when Ephedra alkaloids are combined with other medications that cause increased adrenergic tone, such as bupropion or monoamine oxidase inhibitors (Dingemanse et al., 1996; Lefebvre, et al., 1995). Catecholamines also decrease myocardial refractoriness, which can predispose the heart to arrhythmias, and indeed ventricular arrhythmias have been reported in pregnant women using over-the-counter decongestants (Onuigbo and Alikhan, 1998) as well as in others using Ephedra alkaloids recreationally (Andraws et al., 2005). Cases of stroke in connection with the use of ephedrine and related compounds have been reported (Kaberi-Otarod et al., 2002; Mourand et al., 1999; Stossel et al., 1985; Vahedi et al., 2000; Yin, 1990). Morgenstern et al. (2003) reported a case-control study examining the risk of hemorrhagic stroke associated with these compounds. Overall, they found a trend toward an increased risk at doses 32 mg/d. A similar study of phenylpropanolamine, an alkaloid commonly found in appetite suppressants and cold remedies, found a significant increase in hemorrhagic strokes among women (Kernan et al., 2000). This latter report prompted the FDA to request that drug companies manufacturing products that contain phenylpropanolamine discontinue or reformulate so as to exclude the alkaloid (USFDA, 2005). Lee et al. found toxicity in a line of cultured neurons when they were exposed to various *ma-huang* preparations (Lee et al., 2000).

DEFICIENCY OF YANG (陽)

There are eight principal syndromes in oriental medical material medica. A deficiency of Yang (陽) is one of them. A Yang (陽)-deficiency cold syndrome was induced by hydrocortisone sodium succinate. *Oleum Cinnamomi* and a water extract of *Cortex Cinnamomi* had similar influences on some indices of energy metabolism, endocrine, and immune systems in rats with a Yang-deficiency cold syndrome (Zhang Q, et al., 2011). Eight monoamine neurotransmitters in the hypothalamus of normal and cortisol-induced Yang (陽)-deficiency rats were measured with HPLC-MS. After administration of Yang-strengthening herbs for 4 weeks, monoamine neurotransmitters, such as noradrenaline, adrenaline and dopamine, were significantly increased when compared to those before the treatment with Yang-strengthening herbs. Furthermore, the ratio of dopamine/3,4-dihydroxyphenylacetic acid and serotonin/5-hydroxyindole-3-acetic acid were also increased in both control and Yang-deficiency rats. Yang (陽)-strengthening herbs were able to inhibit the activity of monoamine oxidase in the hypothalamus (Chen et al. 1990). In the hydrocortisone-induced Yang (陽)-deficiency animal model, the researchers compared the variations of 19 biochemistry indexes involving the nervous-endocrine system, immune system, metabolic system and the function of the liver and kidneys (Zhao et al., 2011). Furthermore, electro acupuncture combined with Chinese herbs was a better therapy for the prolapse of a lumbar intervertebral disc of Yang (陽) deficiency and cold coagulation types (Liu et al., 2009). In a study of cancer patients, at different times during one day, temperature changes in patients in the Yin deficiency group fluctuated dramatically (Cai and Li, 1990).

In a deficiency of Yang in the kidneys, there has been interesting research in which hypothyroidism caused by various factors was treated for one year with the Chinese medicinal herb preparation "Shen Lu tablet (SLT)" to warm and reinforce

the Kidney's Yang. The values of serum concentration of total T3 and T4 significantly increased after treatment with SLT, but serum levels of TSH decreased. It is suggested that hypothyroidism is closely related with the deficiency of Kidney's Yang and energy metabolism (Zha, 1993). The warm and tonifying kidney-Yang herbs perform their therapeutic effects by regulating the metabolism, protecting the stability of the mitochondrial membrane and maintaining the signal conduction in the cells (Lu, et al., 2009). In some studies, the metabonomic characteristics of the 'Kidney-Yang Deficiency Syndrome' are induced by high doses of hydrocortisone (Lu et al., 2011; Su et al., 2010). In other research, a Shen-Yang deficiency (SYD) was induced by adenine (Liu et al., 2012), and also in an experiment of SDY animal models, rats were induced by injecting cetacort into their buttocks (Li et al., 2009). A deficiency-Yang syndrome was established by injecting corticosterone (Li et al., 2011). There have been some studies not only about the gene expression profiles in kidney-Yang deficiency (Wei et al., 2011) but also about the non-inflammatory and non-liquefied semen as deficiency Yang symptoms (Xiong et al., 2009). In studies of kidney-Yang deficiency syndrome, it was closely related to the cold syndrome through family investigation and cDNA microarray technology, exploring the effects of both genetic and environmental factors on the health of family members (Wang et al., 2006).

CONCLUSION

Ephedra has been used to treat colds and to provide cough relief for centuries in oriental medicine. The herb remedies in Shan han lun has been used to treat the person after sweating a lot. Recently, it has been reported that Ephedra plays a crucial role in weight loss and the enhancement of athletic performances. However, the overuse of Ephedra causes cardiovascular side effects such as increases in blood pressure, heart rate, and palpitations. The cardiovascular effect from overusing Ephedra is regarded as a deficiency of Yang model, which is one of the eight principal syndromes in oriental medicine. Even though many researches showed that a deficiency of Yang enhanced with treatment of various herbs, more research is needed to clarify the effects of herb remedies on the basis of the traditional medicinal aspects of Shan han lun: to show whether they are really effective for the deficiency of Yang syndrome.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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