

Ma Huang (Ephedrae Herba): Setting the Record Straight

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Abstract

Chinese herbal formulas that contain Ma Huang (Ephedrae Herba, ephedra) have been used safely for two millennia, primarily as anti-asthmatics. They remain in widespread use today in China, Japan and Taiwan, without reported adverse effects. The use of a non-traditional combination of ephedra and caffeine in weight loss products by a susceptible demographic led to the observation of a possible association with cardiovascular toxicity and hepatotoxicity, leading to ephedra's ban in the United States in 2004. This paper reviews the scientific information available about ephedra and proposes mechanisms for the observed adverse effects when it is combined with caffeine. The author also proposes adding obesity and Metabolic Syndrome to the list of cautions and possibly contraindications to the use of Ma Huang.

Introduction

Note: The terms Ma Huang and ephedra are used interchangeably in this paper. These terms, in pinyin and English respectively, refer to Ephedrae Herba, the ephedra stem.

Contemporary Chinese medicine is rooted in texts from as far back as the third century BCE. These texts have been compared to the Hippocratic writings. Whereas modern medicine has reduced Hippocrates to the 'honoured originator of a tradition that has become obsolete' (Unschuld, 2003, p.ix), physicians and researchers continue to refine their understanding and use of the medicinal substances in the Chinese Materia Medica. According to the National Institute of Health (NIH), between 1995 and 1997 the Food and Drug Administration (FDA) received over 900 reports of ephedra-associated adverse events, which included a total of 37 cases of stroke, heart attack and sudden death (NIH, Ephedra Fact Sheet). Ephedra was completely banned in the United States in 2004. Ephedra use can cause adverse effects at any dose when combined with other drugs such as caffeine, as found in guarana, kola nut and yerba mate, or salicylates, as found in willow bark. While there is no reason to believe that this ban will be lifted, it is important to understand what went wrong with ephedra use in the United States. It is equally important to understand how ephedra continues to be safely used today outside the United States and Europe.

History of Ma Huang

Ma Huang, which means hemp yellow (Chen & Chen, 2012, p. 36), the dried stem of the ephedra plant, was first documented in *Shen Nong Ben Cao Jing* (The Divine Husbandman's Classic of Materia Medica), ca.200-250 CE (see figure 1). It was considered a 'middle class' medicinal, a substance that is used to treat disease, and it is not used for a prolonged period of time. It is described as a strong acrid (dispersing), slightly bitter and warm herb that 'effuses the exterior [through] sweating, eliminates evil heat qi, suppresses cough and counterflow qi ascent, eliminates cold and heat, and breaks through concretions and hardness, accumulations and gatherings' (Yang, 2012, p.51). 'Acrid medicinals act upon the lung' (Wiseman & Feng, 1998, p.5), and Ma Huang is a yang medicinal (ibid., p.17) used to diffuse 'inhibited lung qi' (ibid., p.128). It is classically used to treat greater yang channel disease characterised by contraction of wind-cold without sweating. In Li Shi-Zhen's *Ben Cao Gang Mu* (Compendium of Materia Medica), Chinese Ming Dynasty (1368-1644), Ma Huang is classified as an anti-asthmatic and a 'circulatory stimulant' (Chen & Schmidt, 1926, p.4).

In Zhang Zhong-Jing's *Shang Han Lun* (On Cold Damage), late Chinese Han Era (ca. 200 BC-200 AD), it is stated that the foam or froth produced when Ma Huang is boiled is to be removed prior to adding other ingredients (line 35). The author did not state why. The earliest recorded evidence we have that Ma Huang has a stimulatory effect is derived from

the use of the word 'fan' (煩, whose radical, 火, means fire), meaning vexation, irritation or restlessness, used to describe symptoms associated with the consumption of the foam or froth created when Ma Huang is boiled. The word was originally used in the *Shen Nong Ben Cao Jing Ji Zhu* (Collection of Commentaries on the Classic of the Materia Medica), a commentary and expansion upon the *Shen Nong Ben Cao Jing* by the scholar Tao Hong-Jing (456-536) in the Northern Qi Dynasty, ca. 494 (chapter 2, middle group). Bensky (2004, p.7) cites *De Pei Ben Cao* (Materia Medica of Combinations, 1761) written by Yan Jie, Shi Wen and Hong Wei as saying that 'the froth 'makes one irritable'; however, 'frying with honey before use will also work' to prevent these side effects. Mitchell, Feng and Wiseman (1999, p.92) state in their contemporary translation and commentary of the *Shang Han Lun* that 'the foam produced when ephedra is boiled is traditionally removed because it is thought to cause vexation.'

In the practice of Chinese medicine and according to current Chinese Materia Medica textbooks, the uses of Ma Huang are as follows: it releases the exterior through diaphoresis, relieves wheezing, dyspnoea and cough, regulates water circulation, relieves oedema, and disperses cold (Chen & Chen, 2012, p.36; Bensky, 2004, p.4).

Pharmacologically, Ma Huang has sympathomimetic effects on the cardiovascular system and smooth muscles of the bronchi, as well as diaphoretic, anti-pyretic, anti-

inflammatory and anti-allergic effects (Chen & Chen, 2012, p.38; Bensky, 2004, p.7; Zhu, 1998, p.47). There are about 50 Ma Huang species, those referred to here, containing the alkaloid ephedrine, are *Ephedra sinica* (E. Sinica), *Ephedra intermedia* (E. Intermedia) and *Ephedra equisetina* (E. Equisetina) (Zhu, 1998, p.45). E. Sinica has historically been the most commonly used Ma Huang species in Chinese medicine.

History of ephedrine

In 1885 ephedrine was isolated as the active ingredient of Ma Huang by the Japanese chemist, Professor Nagayoshi Nagai. Pseudoephedrine was discovered two years later (see figure 2). In 1913 it was discovered that ephedrine is a sympathomimetic catecholamine similar in action to, but weaker in effect than, epinephrine (the adrenal hormone adrenaline). In small doses it acts as a stimulant, raising blood pressure and heart rate by causing peripheral vasoconstriction, and it relaxes bronchial smooth muscles, thereby increasing respiratory volume and producing an anti-asthmatic effect. Chen & Schmidt remark that, in a healthy heart, 'if the vagi are intact, the heart may be slowed reflexly as pressure rises, though amplitude is increased' (Chen & Schmidt, 1959, p. 606). In large doses it is a depressant, it lowers blood pressure and causes heart failure.

The adverse effects of small doses of ephedrine are caused by three mechanisms. It stimulates the sympathetic nervous system in the kidneys causing vasoconstriction of the renal arteries and a spillover of the protein albumin from the blood into the urine (albuminuria); it stimulates the central nervous system causing insomnia, sweating, nausea, palpitations and tremors; and it increases sympathetic tone, exacerbating hypertension or inducing arrhythmias in patients with coronary artery disease. If taken in large doses ephedrine depresses the cardiovascular system causing arrhythmia and cardiac failure (Chen & Schmidt, 1959, p.614).

Professor Nagai's discovery of ephedrine remained unheralded in the West. Independently, Ko Kuei Chen and Carl F. Schmidt discovered ephedrine in the 1920s. In 1926 ephedrine was submitted to and approved by the American Medical Association. Chen and Schmidt write: 'One of the interesting aspects of the usefulness of ephedrine, as established by modern clinicians and experimenters, is that it justifies the Chinese tradition concerning Ma Huang in many respects' (Chen & Schmidt, 1930, p.6). This most likely refers to its use as an anti-asthmatic, relieving bronchospasm and to its diaphoretic action through its effects on the central nervous system, and possibly through stimulation of the stellate (cervicothoracic) sympathetic ganglion.

Ephedrine's clinical applications can be summarised as follows: it is a mydriatic used to dilate the pupils for



Figure 1: Illustration of Ma Huang (stem)

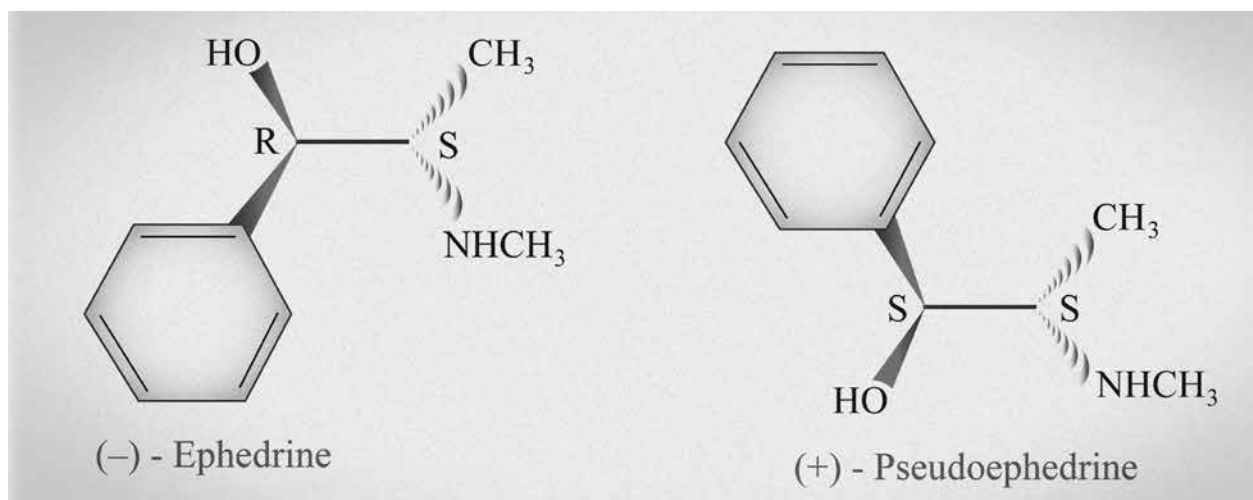


Figure 2: Ephedrine and pseudoephedrine chemical structure

fundusoscopic examination; it astringes mucous membranes and is used for acute and chronic rhinitis; it is a circulatory stimulant in the absence of cardiac disease; it dilates the bronchioles and is used in the treatment of asthma; and it raises basal metabolic rate (Chen & Schmidt, 1959, pp. 610-613). 'A curious feature in the action of ephedrine in asthmatic patients is that it usually dilates the bronchioles without raising systemic blood pressure, while a similar dose regularly raises blood pressure in nonasthmatic patients. The difference must be due to an effect on the pulmonary circulation' (ibid, p. 613).

Ephedrine is primarily excreted through the kidneys as an unchanged drug within 24 to 48 hours (Sever, 1975). Four to 20 per cent is metabolised in the liver through deamination and demethylation into benzoic acid, hippuric acid, norephedrine (also known as phenylpropanolamine) and p-hydroxyephedrine (which is inactive) (Feller, 1977).

Ephedrine and adrenaline are very similar in chemical structure. Adrenaline was the primary drug used in the treatment of acute asthma until ephedrine was discovered. Ephedrine was considered the anti-asthmatic of choice because of its stability, it can be given orally and has a more prolonged effect. By contrast, adrenaline is rapidly oxidised and rendered inactive, has to be given by intramuscular injection, is rapidly destroyed by enzymes in the gastrointestinal system rendering its therapeutic lifespan short-lived, and its use can result in bronchospasm, hypoxia and ventricular arrhythmia. Between 1930 and 1940 ephedrine was considered the anti-asthmatic of choice before it was replaced by albuterol (Lee, 2011). Nowadays the conventional treatment of asthma is with selective beta-2 adrenergic bronchodilators such as albuterol sulfate (salbutamol), leukotriene modifiers such as montelukast sodium (Singulair), and inhaled corticosteroids.

Because of its pharmacological effects, which appear to be primarily adrenergic or sympathomimetic, ephedrine use is contraindicated in patients with hypertension,

arrhythmias, cardiovascular diseases, glaucoma, diabetes (it can increase plasma glucose and fasting insulin levels), prostatic hypertrophy (it causes vasoconstriction of the renal arteries and constriction of the urethral sphincter) and hyperthyroidism (Zhu, 1998, p.50; Chen & Chen, 2012, p.37). Ephedrine has a moderate beta and weak alpha adrenergic stimulation effect that increases cardiac output and blood pressure, and decreases renal perfusion. Ephedrine use is contraindicated in patients on certain prescription drugs such as norepinephrine-dopamine reuptake inhibitors (NDRIs) like bupropion, monoamine oxidase inhibitors (MAOI) like phenelzine, and beta-blockers like propranolol. In the 1930s it was already established that an overdose could result in cardiac failure and hyperthermia.

Both ephedrine and pseudoephedrine are bronchodilators, but the former is more than twice as potent. It takes three times as much pseudoephedrine compared to ephedrine to raise diastolic blood pressure above 90 mmHg. Pseudoephedrine is most commonly used as a nasal decongestant in cough and cold medications (Haller, 2000).

Metabolism and detoxification of drugs

Cytochrome P450 (CYP) enzymes are involved in the metabolism and detoxification of drugs and environmental pollutants. Altered plasma drug concentrations can occur when another substance either induces (enhances) or inhibits (slows) CYP enzymes that share the same pathway. Phase 1 metabolism occurs predominantly in the liver, and this system is genetically determined. Together, Phase 1 and Phase 2 enzymes usually detoxify drugs and environmental pollutants. However, CYP enzymes can also transform relatively innocuous substrates into hepatotoxins, carcinogens or mutagens. An example of this is the transformation of charred meat into a carcinogen.

Caffeine, alcohol, oral contraceptives, ephedrine and theophylline are examples of substances and drugs that

share the Phase 1 CYP 1A2 metabolic pathway to excretion. Any drug or substance that inhibits the CYP 1A2 system will increase the plasma concentrations of other drugs and substances that share the CYP 1A2 system. Conversely any drug or substance that induces the CYP 1A2 system will reduce the plasma concentrations of drugs sharing this pathway. Cigarette smoking induces or increases CYP 1A2 activity, thus asthmatics taking theophylline - a commonly used anti-asthmatic - have increased dose requirements. Induction of the CYP 1A2 enzymes by alcohol can result in a fatal hepatotoxic accumulation of the metabolic by-products of acetaminophen (paracetamol) breakdown. Oral contraceptives inhibit CYP 1A2 activity: the half life of caffeine in subjects taking oral contraceptives is 10.5 hours compared to 5.5 hours in subjects not taking oral contraceptives. CYP 1A2 activity can vary up to 40-fold between individuals (Faber, 2005) based on gender and ethnicity (Relling, 1992), and there are significant differences in the metabolism of environmental chemicals that share the CYP 1A2 system that can result in increased toxicity in various organ systems including the liver (Nebert & McKinnon, 1994).

Ephedra by itself has been shown to induce activity of the CYP 1A2 system and pseudoephedrine to inhibit it. The product *Shoseiryuto* (*Xiao Qing Long Tang* [Minor Bluegreen Dragon Decoction]), containing ephedra, has not been shown to cause pharmacokinetic interactions with medications dependent on the same pathway (Nakao, 2007). By contrast, caffeine and liquorice (*Gan Cao*, *Glycyrrhizae Radix*) induce CYP 1A2 activity. Ephedra Water Decoction (single herb) and Moxing Cough Tablets (containing ephedra, apricot kernel, gypsum and liquorice, similar to *Ma Xing Shi Gan Tang* [Ephedra, Apricot Kernel, Gypsum, and Liquorice Decoction]) are both shown to induce activity of the CYP 1A2 system thereby altering the metabolism of theophylline (Tang, 2012). These studies, although limited in number, illustrate that the induction of the CYP 1A2 enzymes could also be dependent on the specific combination of herbs or drugs.

In summary, caffeine and ephedra may increase the rate of liver clearance of other drugs and chemicals dependent on the CYP 1A2 pathway. An obese population with potential co-morbidities might be taking prescription drugs. Unaware of possible drug interactions in taking an over-the-counter product for weight loss, this population is at risk of altered plasma levels of prescription drugs.

Some of the potent inhibitors of CYP 1A2 enzyme activity are cimetidine, a histamine H2 receptor antagonist that inhibits stomach acid production, the antibiotics ciprofloxacin and enoxacin and the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. Potent CYP 1A2 inducers are smoking, the antimicrobial rifampin used to treat tuberculosis, and barbiturates, which are central nervous system depressants used to treat anxiety, depression, insomnia and seizures.

Pharmacodynamics of Ma Huang

The aerial parts of the Ma Huang species contain 0.02 to 3.4 per cent of six alkaloids: ephedrine, pseudoephedrine (the major alkaloids) and N-methyl ephedrine, N-methylpseudoephedrine, norephedrine and norpseudoephedrine (the minor alkaloids). Thirty to 90 per cent of the alkaloid content is ephedrine (Abourashed, 2003). The major pharmacological effects of Ma Huang, bronchodilating and vasoconstricting, are attributable to ephedrine and pseudoephedrine respectively. The isomers norephedrine (a stimulant) and norpseudoephedrine (a decongestant) are two phenylpropylamines (PPA). According to the *Japanese Pharmacopoeia* XVI (2011, p.1637), the dried stem of *E. Sinica*, *E. Intermedia* and *E. Equisetina* contain no less than 0.7 per cent of total alkaloids as ephedrine and pseudoephedrine. The *Pharmacopoeia of the People's Republic of China* (2010, pp. 300-301) states that Ma Huang contains no less than 0.8 per cent alkaloids. An anti-inflammatory alkaloid called ephedroxane, small amounts of essential oils, tannins and flavonoids have also been isolated from the above-named species.

The alkaloids ephedrine and pseudoephedrine should not be confused with the herb ephedra, much like caffeine should not be confused with coffee or tea.

Normotensive subjects experience benign pharmacodynamic cardiovascular responses from the ingestion of four capsules of powdered Ephedra sinica, 375 milligrams each twice per day, for a total of 40 milligrams of ephedrine per day, without any side effects (White et al., 1997). The typical dose of ephedrine for bronchodilation is 25-50 milligrams in adults and 25 milligrams in children. It takes a mean dose of 75 milligrams of ephedrine or 210 milligrams of pseudoephedrine to raise diastolic blood pressure above 90 mmHg, and systolic blood pressure to 171 mmHg and 155 mmHg respectively (Drew et al., 1978).

The alkaloids ephedrine and pseudoephedrine should not be confused with the herb ephedra, much like caffeine should not be confused with coffee or tea. Ephedra also contains ephedroxone, tannins, essential oils and flavonoids. 'Absorption of ephedrine from the gastrointestinal tract is relatively complete' (Barceloux, 2008, p.547), although the absorption rate from consuming ephedra is much slower than from ephedrine. It takes ephedra in powdered form (*E. Sinica*) 3.90 hours to release its maximum concentration of ephedrine into the bloodstream compared to 1.69 hours for an ephedrine tablet and 1.81 hours for an ephedrine solution. While the total maximum plasma concentration of ephedrine reaches the same levels, White et al. state 'in vivo extraction of ephedrine from the plant matrix is a step that limits the rate of absorption' (White, 1997).

M.R. Lee in *The History of Ephedra* (Ma Huang) writes, 'Ephedra and ephedrine deserve an honored place in the history of pharmacology and therapeutics. To paraphrase the ancient Roman poet Horace, the abuse of a substance does not weigh against its right or proper use' (Lee, 2011).

What went wrong: cardiovascular toxic and hepatotoxic effects

Ephedrine is lipophilic and readily crosses the blood-brain barrier. As a central nervous system stimulant, it purportedly enhances athletic performance by decreasing the perceived rate of exertion; however, while this claim is still widely held by athletes, it remains unsubstantiated in controlled trials (Haller & Benowitz, 2000). Effects of ephedrine on the brain stem include insomnia, tremors, and stimulation of the respiratory and vasomotor centres of the medulla. Ephedrine is relatively easily converted to methamphetamine and used as a street drug. As a weight loss supplement often synergistically stacked with caffeine, it is associated with modest short-term weight loss benefits. However, in weight loss products where ephedra is combined with caffeine, there is a reported two to three fold increase in psychiatric symptoms, autonomic symptoms, upper gastrointestinal symptoms and heart palpitations compared to either caffeine or ephedrine alone (Shekelle, 2003). Studies indicate that the interactions between ephedrine and caffeine are primarily pharmacodynamic rather than pharmacokinetic (Barceloux, 2008, p.548; Haller et al., 2004), in other words their mechanisms and sites of action are different. Caffeine increases systolic blood pressure via adrenomedullary catecholaminergic action, and ephedrine increases heart rate via beta-adrenergic receptor activity. This combination of a vasopressor and chronotropic effect from caffeine and ephedrine respectively amplifies the increase in blood pressure.

In in vivo human studies, urinary catecholamine levels are not increased following the administration of 25 milligrams of ephedrine and this suggests that ephedrine's effects are mediated by a direct adrenergic response (Haller et al., 2004). Caffeine increases plasma free fatty acid (FFA) levels via a catecholaminergic mechanism and ephedrine increases FFA levels via beta-adrenergic effects which, in combination, are additive. The subjective 'high' resulting from the combination exceeds stimulation levels from caffeine and ephedrine alone. In summary, ephedrine and caffeine have additive synergistic effects on systolic blood pressure, heart rate, fasting glucose, insulin, lactate, FFA concentrations as well as subjective stimulant effects (Haller et al., 2005) (see Table 1).

Physical & Subjective Response	25 mg Ephedrine	200 mg Caffeine	Ephedrine + Caffeine
Heart Rate	↑↑	↔	↑↑
Blood Pressure	↔	↑	↑↑
Plasma Glucose	↑↑	↔	↑↑
Fasting Insulin	↑	↔	↑↑
Insulin resistance	↑	↔	↑↑
Free Fatty Acids	↑	↑↑	↑↑
Plasma Lactate	↔	↑	↑
Urine Epinephrine	↔	↑↑	↑↑
Energy	↔	↑↑	↑↑
Restlessness	↔	↔	↑↑
Feeling High	↔	↔	↑↑

Table 1: Enhanced stimulant and metabolic effects of combined ephedrine and caffeine (Haller et al., 2004) Key: ↑↑ = significant increase; ↑ = increase; ↔ = no change

Ephedra and caffeine were combined and marketed in popular weight loss supplements. 'Product inconsistency' is found in weight loss products containing ephedra alkaloids and caffeine (Haller et al., 2004). The dose of ephedrine in weight loss products is typically 20 milligrams per serving, taken two to three times per day. A dose of 20 milligrams of ephedrine combined with 200 milligrams of caffeine in a typical thermogenic weight loss product increases mean systolic blood pressure by up to 14 mmHg (Haller et al., 2000). The additional unknown factor is how much caffeine is not only in the weight loss product, assuming it is accurately labelled, but also consumed as coffee, tea and soda. Obesity (a body mass index above 30) creates a state of chronic sympathetic activation (Curtis & O'Keefe, 2002) that could render this population more susceptible to sympathomimetic substances (Persky, 2004). In dogs with ischemic heart disease, ephedrine, at over-the-counter doses (0.4 milligrams per kilo per day, as intended for human consumption in the over-the-counter weight loss product Xenadrine) is found to significantly augment cardiac (reflex) sympathetic activity, which is associated with lethal ventricular arrhythmias and sudden cardiac death, as pointed out by Adamson et al. (2004). This study suggests 'that individuals with clinical or subclinical ischemic heart disease are at high risk of ventricular arrhythmias and sudden death during treatment with ephedrine.' In 1924, Chen and Schmidt observed a depressor effect of ephedrine and suggested

that a heart with inadequate blood flow ‘... is more sensitive to the depressant effect of ephedrine, and less responsive to its stimulant effect, than the normal heart’ (Chen & Schmidt, 1959, p.607).

Metabolic Syndrome, which affects approximately 40 per cent of the population in the United States, is a condition associated with obesity, hypertension, dyslipidaemia, insulin resistance, reduced fibrinolysis, hyperuricaemia and hyperglycaemia (Cordain et al., 2003). It is proposed that Metabolic Syndrome is a sympathetic disease, characterised by adrenergic overdrive, as demonstrated by ‘elevated urinary noradrenaline levels, increased efferent muscle sympathetic nerve activity, and elevated rates of plasma noradrenaline spillover’ even in the absence of hypertension (Schlaich et al., 2015). ‘Interestingly, sympathetic overdrive is detectable in obese patients prone to Metabolic Syndrome before hypertension occurs. Also, when obesity and hypertension are both present in the same patient, the degree of sympathetic activation is much greater than in those with either condition separately’ (Canale et al., 2013). Researchers have suggested moderating the effects of the sympathetic nervous system through weight loss, diet and exercise (which decreases sympathetic tone and increases parasympathetic vagal tone) as a treatment strategy to improve cardiometabolic risk in obesity (Lambert et al., 2015).

The combination of two doses separated by five hours each of 25 milligrams of ephedra alkaloids and 200 milligrams caffeine, such as in the weight loss product Xenadrine, is particularly unfavourable in the obese sympathetically over activated population; it causes sustained increases in blood pressure and heart rate, increases in plasma glucose and insulin, and decreases in potassium (Haller et al., 2005). The effects of ephedrine and caffeine alone are modest. Twenty-five milligrams of ephedrine alone increases heart rate, plasma glucose and fasting insulin concentrations, but not systolic blood pressure (it decreases diastolic blood pressure); 200 milligrams of caffeine alone increases systolic blood pressure, plasma free fatty acid and urinary epinephrine concentrations but does not increase heart rate (Haller & Benowitz, 2004).

A 2002 observational study reported that cardiovascular toxic effects of Ma Huang were not limited only to large doses or pre-existing cardiovascular disease (Samenuk et al., 2002). However, because of a lack of appropriately designed toxicity studies, the authors duly noted that the cases only revealed a temporal, not causal relationship between the use of Ma Huang and adverse cardiovascular events. The additional stimulants subjects were consuming, such as caffeine, were not reported. The products containing Ma Huang were being used for weight loss, energy enhancement, bodybuilding and recreational activities.

Barceloux (2008, p.547) writes that ‘the relatively low rate of serious adverse effects compared with the high

rate of use of these herbs suggests these adverse events may have a pharmacogenetic or idiosyncratic etiology,’ and ‘most of the case reports of serious cardiovascular or cerebrovascular complications involve the use of Ma Huang or ephedrine-containing herbal preparations in excessive doses for prolonged periods.’

It would be interesting to know whether these cardiovascular events occurred during the early morning hours that correspond to the circadian rise in sympathetic activity. An elevated resting heart rate of more than 90 beats per minute is a strong predictor of cardiovascular disease and mortality. The inability to reach 85 per cent of age-predicted peak maximum heart rate on a treadmill test, failure to rapidly decrease heart rate after exercise, and low heart rate variability are all signs of chronic sympathetic overload on the cardiovascular system. Interventions such as moderate regular exercise, omega-3 fatty acids, the Mediterranean and Palaeolithic diets, ACE inhibitors and beta-blockers can be used to modulate sympathetic function in patients at increased risk. Chronic sympathetic activation is caused by obesity, hypertension, depression, anxiety, sleep apnoea, chronic stress, smoking, an unhealthy diet and the abuse of stimulants (Curtis & O’Keefe, 2002).

In 2000 the New England Journal of Medicine published results of the Hemorrhagic Stroke Project. The study reported that use of two major formulations of PPAs, primarily appetite suppressants and stimulants (norephedrine) and possibly decongestants in cough and cold remedies (norpseudoephedrine) posed independent risk factors for non-traumatic haemorrhagic stroke in women (Kernan, 2000). A case-control study on ephedra use within three days of developing a haemorrhagic stroke did not detect a statistically significant increase in the risk of haemorrhagic stroke with ephedra use, but a higher odds adjusted ratio from consuming more than 32 milligrams per day. Very specifically this study reported: ‘Although the overall results do not indicate an association between the use of ephedra-containing products and increased risk for hemorrhagic stroke, the analysis by dose suggests there may be an association with use of more than 32 milligrams per day.’ The study reported that 84 per cent of the subjects were taking ephedra plus a stimulant such as caffeine (Morgenstern, 2003). The pathophysiology behind this event is a proposed catecholaminergic-induced increase in blood pressure as well as possible changes in platelet aggregation leading to an increased potential of bleeding. Watson et al. report that ‘sympathomimetics significantly alter platelet function, and they may increase the potential for bleeding independently of their effects on blood pressure’ and that ‘caffeine enhances the effect of ephedrine on platelet function’ (Watson et al., 2010). Compared to controls, patients in this study were more likely to report a family history of haemorrhagic stroke, suggesting a possible increased susceptibility.

'Many of the case reports associating cardiovascular or neurological complications with Ma Huang use indicate possible causal effects rather than probable causal effects based on the Naranjo Adverse Drug Reaction Probability Scale' (Barceloux, 2008, p.548). It is possible that the adverse side effects may be related to the additive effects of caffeine, contraindications to the use of ephedra and ephedrine, individual susceptibility and pre-existing medical conditions (Haller & Benowitz, 2000).

Reports also emerged of hepatotoxicity, including acute hepatitis (hepatocellular damage) and acute liver failure, from using weight loss products such as Xenadrine, Exceleator, Thermolite, BetaLin, Hydroxycut, Thermo Diet Stack and Metabolife 356 with ephedra as an ingredient. In one report, the time to symptom development ranged from four weeks to 156 weeks, and time to recovery ranged from four weeks to eight weeks. In the same report, the one patient who died had been using Exceleator for four weeks and the patient who had been using Xenadrine for 156 weeks, who also had significantly higher liver enzyme levels, recovered. Two patients required liver transplants; one had been using Metabolife 356 for 16 weeks and the other Thermo Diet Stack for 4 weeks. Morbidity did not correlate to either length of time of product usage or absolute liver enzyme levels. The authors state that while the potential of prior liver disease such as fatty infiltration or fibrosis from obesity could not be excluded, an 'idiosyncratic' or unknown mechanism of liver injury may have occurred because hypersensitivity reactions to the product were not experienced and ephedrine is primarily excreted through the kidneys as an unchanged drug. In the majority of cases, liver enzyme levels returned to normal within a few months of discontinuing use of the ephedra-containing product (Neff et al., 2004).

A prolonged half-life of ephedra due to early liver failure and decreased liver metabolism has been suggested as a mechanism of hepatotoxicity. It is possible that the susceptible patients had a genetic polymorphism that altered CYP 1A2 activity. They could have had an autoimmune aberration resulting in hepatocellular damage. In using ephedra for weight loss, it is also possible that fat-soluble toxins (such as xenobiotics) stored in and metabolised from adipose tissue induced CYP enzymes that damaged the liver. And finally, there could have been contaminants in the products consumed. No published studies have to date been able to biochemically explain the mechanism of hepatocellular damage from ephedra use. In the United States, the reports of adverse events associated with ephedra-containing dietary supplements and a high profile fatality associated with the use of ephedra in a weight loss product in 2003 led to a ban on ephedra by the FDA in April 2004. Ephedra was not banned because of its use as a bronchodilator or anti-asthmatic in Chinese herbal formulas; ephedra was banned because of its

misuse as a stimulant and weight loss product, when combined with caffeine, in a population suffering from chronic sympathetic overactivation, a condition that is very common in today's obese society (see aside box).

A patient with Metabolic Syndrome who presented for acupuncture

This was a patient seen in the author's clinic in 2015, who presented for acupuncture for knee pain. Her past medical history was noteworthy. She had tried various over-the-counter weight loss products for years; in her words she had 'tried everything', including ephedra-containing products when they were still available. This is the profile of a patient with Metabolic Syndrome who should not have been using a sympathomimetic product. I propose that hers is not unlike the profile of many other weight loss product users.

41 Year old female

Chief Complaint: Left sided knee pain

Height: 5 foot 1 inch

Weight: 230 lbs

BMI: 43.5

BP: 148/90

Resting heart rate after 15 minutes in a relaxed setting: 92 BPM

Prescription medications: Lisinopril, Hydrochlorothiazide (she admitted she forgot her medications that morning and thought that might explain why her blood pressure was so high).

Past medical history: Significant for polycystic ovarian syndrome, severe pre-eclampsia and an emergency caesarean section, depression and anxiety.

Laboratory findings: C-reactive protein CRP 6.3 H (reference range < 1 mg/L), HbA1c: 5.8 H (pre-diabetic, reference range < 5.7 %), HDL 34 L (reference range > or = 46 mg/dL), Chol:HDL ratio 5.3 H (reference range < 5.0 mg/dL), Vitamin D 27 L (reference range varies depending on lab 30-100 ng/mL).

Current uses of Ma Huang

Although ephedra was banned in the United States, ephedra-containing formulas continue to be widely and safely prescribed by physicians in anti-asthmatic formulas in China, Japan and Taiwan, where commonly prescribed herbal formulas in granule form are regulated by the same agencies that regulate the pharmaceutical industry. In China, individual herbs are prepared separately with autonomous quality control and then combined according to the formula being prepared. Japan has pioneered

standardised granule 'Kampo' formulas. The Japanese Pharmacopoeia lists 165 approved herbal ingredients, and 210 formulas are approved as ethical drugs, which are prescribed by medical doctors and reimbursed by insurance companies. The formulas are standardised by high performance liquid chromatography (HPLC) to have consistent levels of two-three bioactive markers.

The *Japanese Pharmacopoeia XVI Supplement II* (2014, p.2786) lists Maoto Extract (Ma Huang Tang [Ephedra Decoction]) with the following ingredients: Ma Huang (Ephedra Herba) 5g, Xing Ren (Armeniacae Semen) 5g, Gui Zhi (Cinnamomi Ramulus) 4g and Gan Cao (Glycyrrhizae Radix) 1.5g. Very specifically, it states 'Maoto Extract contains not less than 15 mg and not more than 45 mg of total alkaloids [ephedrine and pseudoephedrine], not less than 48 mg and not more than 192 mg of amygdalin [from Xing Ren], and not less than 14 mg and not more than 42 mg of glycyrrhizic acid [from Gan Cao], per extract prepared with the amount specified in the Method of Preparation.'

In Japan, each batch of formula comes with a quality control certificate and HPLC monograph effectively demonstrating that the active ingredients are within the standardised range of specifications. HPLC testing of raw materials and finished granule products also eliminates the risk of toxic heavy metal contamination. Pharmaceutical Good Manufacturing Practice (GMP) is required of the companies manufacturing granule herbs. In China, six companies are licensed by the SFDA (State Food and Drug Administration) to produce compound granule herbs. The clinical efficacy of formulas made by combining granules of individual herbs, such as practised in China, has been found to be equal to that of formulas where all the raw ingredients are processed together, as in Japan (Luo et al., 2012). Herbal formulas from both countries are the result of quality controlled industrial production and are screened for active ingredient dose consistency. Central agencies are in place for prescribers to report side effects or adverse effects from the use of formulas in Japan and China, including those from raw herb formulas. Therefore it is safe to conclude that adverse reactions to ephedra-containing formulas are not occurring at a rate or severity to cause concern.

How Ma Huang is safely used in Chinese medicine

With the exception of *E. Intermedia*, where the ratio is reversed, the ephedrine to pseudoephedrine ratio in *E. Sinica* and *E. Equisetina* is approximately 2:1 (Zhu, 1998) (see table 2). Formulas containing the upper range of 45 milligrams of ephedrine and pseudoephedrine per day (at a 2:1 ratio, 30 milligrams of ephedrine and 15 milligrams of pseudoephedrine) are being safely prescribed as anti-asthmatics in China, Japan and Taiwan. This is less than the standard therapeutic Western medicine dose of 50

milligrams for ephedrine, with the difference of course that Chinese medicine does not under any circumstances prescribe ephedrine or ephedra as a single herb.

Ephedra Species	Total Alkaloids	Ephedrine	Pseudoephedrine
<i>E. Sinica</i>	0.487-1.382 %	55-78%	12-23%
<i>E. Equisetina</i>	2.093-2.436%	53-58%	19-27%
<i>E. Intermedia</i>	1.059-1.564%	12-31%	59-75%

Table 2: Constituents of different species of Ephedra, elaborated from Zhu, Y., *Chinese Materia Medica: Chemistry, Pharmacology and Applications*, p.45

There are possible reasons why the use of Ma Huang in Chinese medicine is safe:

1. The whole herb or Ma Huang stem is used.
2. Ephedra Herba is not used as a single herb or prescribed alone. In traditional and classical formulas, herbs are combined in such a way as to moderate and harmonise their individual effects on the body. A commonly used harmoniser in Chinese medicine formulas, Gan Cao (Glycyrrhizae Radix), is hepatoprotective. There might be a different reaction to ephedra, as measured by blood pressure, heart rate, blood sugar, FFA and insulin, when traditional herbal combinations are used. Western research could shed more accurate light on the effect Chinese formulas have on the body, if traditional herbal combinations were studied.
3. Ma Huang is never combined with another stimulant such as caffeine.
4. In Chinese medicine's 5,000 year old history, ephedra has never been used as a stimulant or to promote weight loss, and it is very specifically only used for short periods of time. The clinical indications of formulas containing Ma Huang have historically been colds, flus, headaches, bronchial asthma, oedema and arthralgias.
5. Very specific preparation and dosage instructions are given for Ma Huang.
6. Contraindications to the use of Ma Huang have been clearly documented (see 'Traditional Contraindications' below).

The functions of Chinese herbs have become clearer through the identification of active ingredients in pharmacological studies and active ingredient assays through HPLC monographs; their use has become safer through pharmaceutical grade manufacturing processes, standardisation and quality control; however, use of the formulas is still guided by pattern-based clinical indications. Unlike pharmaceutical drugs, the known biochemistry of Chinese herbs alone does not define their

clinical application; therefore, ephedra has not been used in Chinese medicine to promote, for example, lipolysis, glycogenolysis, central nervous system stimulation or appetite suppression.

Is there evidence that supports the use of Ma Huang in the Chinese herbal medicine clinic of today? Are there any studies to suggest that the benefit of formulas containing Ma Huang go beyond that of existing pharmaceutical drugs or at least rival them in efficacy?

Designing a robust randomised controlled trial (RCT) on Chinese herbal medicine is challenging because each formula is designed to treat a specific zheng (clinical pattern or syndrome), and this changes during the disease process. The Western linear model of disease cause and effect, with a specific pharmaceutical prescribed to target a singular cause, is very different from the Chinese and Japanese disease model of multiple and mutually interacting medicinals. Herbal formulas are designed to treat a pattern of disease, therefore to remove Ma Huang from a formula and study it in isolation - worse yet extract ephedrine from Ma Huang and study its effects on the body in isolation - presents paradigm incommensurability. This is akin to studying and listening to the music produced by the flute section of an orchestra, and expecting this singular component to reflect the composite sound of the whole ensemble.

In spite of these challenges, in Japan Western evidence-based models of research are used for Kampo, which has led to an expansion of the use of herbal formulas in doctors' offices and hospitals. Similarly, such research is being conducted in China and Taiwan on Chinese herbal medicine. Examples of anti-asthmatic formulas containing Ma Huang that are currently safely prescribed by doctors as herbal prescription medications in China, Japan and Taiwan, and that have undergone recent scientific study

include: *Ma Huang Tang* (Ephedra Decoction), *Xiao Qing Long Tang* (Minor Bluegreen Dragon Decoction), *Ma Xing Shi Gan Tang* (Ephedra, Apricot Kernel, Gypsum, and Licorice Decoction) and *Ding Chuan Tang* (Arrest Wheezing Decoction) (see Table 3). Each of these formulas treats a zheng, also defined as the 'aetiology, pathology and disease location' or 'clinical outcome of the disease' at that particular moment (Yu, 2006).

Ding Chuan Tang (DCT) is cited as the most commonly prescribed formula for adults and children with asthma in Taiwan (Wang et al., 2014; Huang et al., 2013). Another study identifies *Ma Xing Shi Gan Tang* (MXSGT) as the most commonly prescribed Chinese herbal medicine for childhood asthma, followed by *Xiao Qing Long Tang* (Minor Blue Green Dragon Decoction, XQLT) and *Xing Su San* (Apricot Kernel and Perilla Leaf Powder), *Mai Men Dong Tang* (Ophiopogonis Decoction) and *Zhi Sou San* (Stop Coughing Powder) (Chen et al., 2013). DCT results in significant improvement in airway function (Chan et al., 2006) and a reduction in allergen-induced airway inflammation (Kao et al., 2004) in asthmatics. XQLT has immunomodulatory effects, reducing bronchial inflammation in allergen-sensitised mice (Kao et al., 2000; Wang et al., 2012) and reducing airway hyper-responsiveness (Chang et al., 2013).

Further benefits of these Chinese herbal formulas include antiviral effects. MXSGT has been shown to have broad-spectrum inhibitory activity against different strains of influenza A viruses (Hsieh et al., 2012) and the respiratory syncytial virus (RSV) (Chen et al., 2015) as well as the effect of reducing lung microvascular hyperpermeability and inflammation (Ma et al., 2014). XQLT shows anti-influenza A, B, and H1N1 activity (Yamada et al., 1998; Nagai et al., 1996).

Formula Name	Abbreviation	Ingredients	Function
<i>Ma Huang Tang</i> (<i>Ephedra Decoction</i>)	MHT	Ma Huang 9g, Gui Zhi 6g, Xing Ren 9-12g, Zhi Gan Cao 3g	Releases exterior and arrests wheezing
<i>Xiao Qing Long Tang</i> (Minor Blue Green Dragon Decoction)	XQLT	Ma Huang 9g, Gui Zhi 9g, Gan Jiang 9g, Xi Xin 9g, Wu Wei Zi 9g, Bai Shao 9g, Zhi Ban Xia 9g, Zhi Gan Cao 9g	Releases exterior, transforms thin mucus, warms the Lungs and directs rebellious qi downward
<i>Ma Xing Shi Gan Tang</i> (Ephedra, Apricot Kernel, Gypsum and Licorice Decoction)	MXSGT	Ma Huang 12g, Shi Gao 24g, Xing Ren 18g, Zhi Gan Cao 6g	Facilitates the flow of Lung qi, clears heat and calms wheezing by directing rebellious qi downward
<i>Ding Chuan Tang</i> (Arrest Wheezing Decoction)	DCT	Chao Bai Guo 9g, Ma Huang 9g, Zi Su Zi 6g, Gan Cao 3g, Kuan Dong Hua 9g, Xing Ren 4.5g, Zhi Sang Bai Pi 9g, Chao Huang Qin 4.5g, Zhi Ban Xia 9g	Disseminates and redirects Lung qi down, arrests wheezing, clears heat and transforms phlegm

Table 3: Antiasthmatic formulas containing Ma Huang: ingredients, dosages and functions (Bensky et al., 2009)

Ma Huang Tang (*Maoto*, *MHT*) is approved by the Ministry of Health, Labour, and Welfare in Japan as an insurance-covered treatment for influenza virus infection. It has been shown to have antiviral activity, in particular for treatment of the seasonal influenza virus (Nagai et al., 2014; Kubo & Nishimura, 2007), that rivals the efficacy of conventional drugs. It is significantly superior to the antiviral oseltamivir (Tamiflu) and similar in efficacy to zanamivir (Nabeshima et al., 2012). In children with low sensitivity to oseltamivir, *MHT* plus oseltamivir significantly decreased symptom duration (Toriumi et al., 2012). Furthermore, *MHT* has been shown to ameliorate the progression of childhood allergic asthma marked by steroid-resistant eosinophilic inflammation (Saglanı & Lloyd, 2014; and Ma et al., 2014).

Chinese medicine can be combined with conventional drugs in the treatment of seasonal flu to mitigate medication side effects and decrease symptom duration. Oseltamivir for example is associated with side effects such as vomiting, headaches, decreased renal creatinine clearance, encephalopathy and abnormal psychiatric behaviour (Hoffman et al., 2013), and concomitant use of the Kampo formulas *Kakkonto* (*Ge Gen Tang*, Kudzu Decoction) and *Maoto* may both ‘reinforce the anti-influenza effect and reduce the risk of central nervous system adverse effects’ (Ohara et al., 2015).

Western research has also shed light on the safety of Chinese herb combinations and formulas. The toxicity of ibuprofen in laboratory animals is considered to be low. Research data shows that the lethal dose required to kill 50 per cent of test subjects (LD50) is twice as much for Ma Huang compared to ibuprofen, when administered intraperitoneally. The LD50 of ibuprofen in mice via intraperitoneal injection is 320 milligrams per kilogram of body weight (Derelanko, Auletta, 2014, p. 848), whereas the LD50 of (water extracted) Ma Huang is 650 milligrams per kilo (Chen & Chen, 2012, p.39, Zhu, 1998, p. 49). In sharp contrast, the LD50 of a formula such as *Ma Huang Tang* is 28.51 grams per kilo (Chen & Chen, 2009, p.42), which exemplifies the high degree of safety built into the use of a formula. The effects of ephedra and ephedrine alone cannot be used to explain the properties of the formula *MHT*. ‘It is clear that ephedrine is not very toxic, and the margin of safety is comfortably wide,’ (Chen & Schmidt, 1959, p. 609), the LD 50 of ephedrine is 245 milligrams per kilo via intraperitoneal injection in mice (Fairchild, Alles, 1967), and it is also clear that the toxicity of Ma Huang and *Ma Huang Tang* are significantly and exponentially lower respectively. A remarkable study cited by Chen portrays the modulatory effects of all the individual herbs in a formula. In healthy male subjects taking *Ma Huang Tang*, an increase in blood pressure, heart rate, stroke volume and cardiac output was recorded, together with an unprecedented decrease in total peripheral resistance. The authors of the study speculated that although Ma Huang

causes vasoconstriction, Gui Zhi (Cinnamomi Ramulus) has a vasodilatory effect that may explain their findings (Chen & Chen, 2009, p.41).

In summary, these Chinese herbal formulas exhibit local anti-inflammatory effects and anti-allergic effects, as well as key anti-viral properties — a very unique and desirable combination. Ma Huang is an ingredient of all these formulas, which have a multi-dimensional effect on the *zheng* they address, one not attributable to a single active ingredient.

Single herbal combinations

‘Ma Huang is one of the most extensively studied Chinese herbs’ (Chen & Chen, 2012, p.39). The successful treatment of the seasonal flu and asthmatic conditions with Ma Huang-containing formulas has generated interest in the anti-viral and anti-asthmatic properties of its ingredients, as well as on the mechanism of interactions between Ma Huang and the herbs it is typically combined with.

Ma Huang and Xing Ren (Armeniacae Semen) (MX), Ma Huang and Gui Zhi (Cinnamomi Ramulus) (MG), and Ma Huang and Shi Gao (Gypsum) (MS) are traditional pairs. Each of these combinations has unique modulatory effects. MX together improve the bioavailability of amygdalin and prunasin (both contained in Xing Ren). Song et al. (2015) report that the simultaneous administration of the MX pair, such as in *MHT*, decreased the accumulation (speeded up the elimination) of ephedrine alkaloids, and increased the bioavailability (slowed down the elimination) of amygdalin (more than of prunasin), producing a better therapeutic effect with fewer side effects in comparison to the compounds administered alone.

Ma Huang is found to be anti-viral and it is thought that a tannin found in the extract inhibits the virus uncoating (Mantini, 1999). An essential oil in Gui Zhi is shown to inhibit membrane protein synthesis thereby slowing viral replication (Hayashi et al., 2007). In the MG combination, Gui Zhi decreases hyperactivity and sensitisation produced by repeated Ma Huang administration and attenuates oxidative stress induced by Ma Huang. The results of a study reported by Zheng et al. (2015), demonstrate the neuroprotective potential of Gui Zhi in Ma Huang-induced hyperactivity and oxidative damage in the prefrontal cortex of rats when the two are used in combination.

The pair MS, as found in the formula *MXSHT*, has antipyretic and anti-asthmatic properties (Mei et al., 2014; Yuan, 1999).

In summary, Chinese herbal medicine, and specifically formulas containing Ma Huang as an ingredient, offers an attractive alternative treatment modality for acute and chronic asthma because of its long history of safe use, the absence of systemic side effects seen in long term use of Western pharmaceutical bronchodilators and corticosteroids, and because of the multiple

systemic benefits offered (Hong et al., 2011; and Ma et al., 2014). Studies have shown Ma Huang-containing formulas to be safe and effective in the treatment of the seasonal flu, for which Western pharmaceuticals have questionable efficacy and undesirable side effects.

Current substitutes for Ma Huang in the United States include Bai Qian (*Cynanchi Stauntonii Rhizoma*), Fang Feng (*Saposhnikovia Radix*), Jing Jie (*Schizonepetae Herba*) and Zi Su Ye (*Perillae Folium*). However, none of these herbs have the same anti-asthmatic and anti-pyretic qualities as Ma Huang – nor do they match it in terms of releasing the exterior and calming wheezing – and thus, in countries where it is not banned, Ma Huang continues to be used because of its superior effects.

The nontraditional combination of ephedra and caffeine in weight loss products and its use by a sympathetically upregulated obese population likely led to the adverse events.

Traditional contraindications

Ma Huang is a diaphoretic and a diuretic. Zhang Xi-Chun stated, 'Ephedrae Herba treats the pathogen in the greater yang Channel by inducing sweating, and the pathogen in the greater yang Organ by releasing it through urination' (Bensky, 2004, p.4). The *Ben Cao Hai Li* (Harm and Benefit in the Materia Medica, 1893) recommended that the dosage of Ma Huang be adjusted to the climate in which the patients live: lower doses where the weather is warm and people sweat easily, and higher doses where the weather is cold and sweat is more difficult to produce. 'From the end of spring through summer until the beginning of autumn, the standard approach is to forbid it; only in the winter when symptoms appear, showing that a truly cold pathogen has injured the nutritive [level], is it of benefit. If not during the winter months, or the symptoms are not those of a cold pathogen, or are those of a cold pathogen in the interior, or those of pathogenic wind injuring the protective [level] then Ephedrae Herba is not suitable, even though there may be fever and chills: there will not be aching and stiffness of the head and body, and no floating and tightness in the six pulse positions' and furthermore 'when the condition is right for sweating, it must not be excessive' (Bensky, 2004, p.7). The use of Ma Huang-containing formulas for the treatment of colds and flus should be discontinued as soon as therapeutic results are achieved. According to the *Shang Han Lun*, where the use of Ma Huang-based exterior-releasing formulas is elaborated upon, the use of MHT is contraindicated in patients with a 'debilitation of fluids and vacuity of blood, insufficiency of fluids and lower burner heat, debilitation of qi and blood, and yang qi or yang vacuity and yin damage' (Mitchell et al., 1999, p.100).

Thirteen formulas out of the 130 discussed in the *Shang Han Lun* contain Ephedra as an ingredient. There is no record of the use of Ephedra as a single herb and this practice continues today.

Ma Huang use and navigating diseases of modern civilisation

Formulas for the treatment of asthma, colds and the seasonal flu that contain Ma Huang and strictly adhere to the composition and dosages given in traditional formulas have been demonstrated to be both safe and effective by the long history of their use, the breadth of their current applications and the lack of adverse reports to regulatory agencies in China and Japan. Observational studies have reported a possible causal relationship between ephedra and adverse cardiovascular events and hepatotoxicity when used with caffeine for weight loss. The non-traditional combination of ephedra and caffeine in weight loss products and its use by a sympathetically upregulated obese population likely led to the adverse events.

The right to dispense Ma Huang-containing formulas should be limited to licensed practitioners of Chinese medicine who have studied its clinical indications and contraindications. A reliable method for physicians to monitor patients' individual reactions to herbal products is not only to monitor symptom progression, but also blood pressure and if necessary, liver enzymes. However, used correctly, for the treatment of acute asthma, colds and the flu, Ma Huang-containing formulas are generally discontinued after about a week and this length of time of use should not necessitate liver enzyme testing. In Chinese medicine the prescription changes following changes in the pattern of disease, therefore chronic conditions such as asthma are often treated with a variety of different formulas during their course. For example, asthma characterised by a pattern of invasion of the Lung by exterior wind-cold with internal phlegm-rheum could be first treated with Ma Huang-containing *XQLT*. After the acute external symptoms abate, the prescription could be changed to *Ling Gan Wu Wei Jiang Xin Tang* (Poria, Licorice, Schisandra, Ginger, and Asarum Decoction) or *Ling Gui Zhu Gan Tang* (Poria, Cinnamon Twig, Atractylodes, and Licorice Decoction) to manage the underlying chronic deficiency-cold condition, or *Shen Ling Bai Zhu San* (Ginseng, Poria, and White Atractylodes Powder) if the underlying condition is Lung and Spleen qi deficiency with accumulation of phlegm-dampness. None of these formulas contain Ma Huang as an ingredient.

Signs of Metabolic Syndrome, hyperinsulinaemia, insulin resistance and hyperglycaemia constitute reasons to consider using a substitute for Ma Huang. This author proposes adding obesity and Metabolic Syndrome, characterised by a state of chronic sympathetic over activation, to the list of cautions and possibly contraindications to the use of Ma Huang. Markers of

excessive sympathetic activity are a resting heart rate above 90 beats per minute, abnormal heart rate recovery after exercise, abnormal heart rate variability and an inability to achieve 85 per cent of predicted maximum heart rate during routine treadmill exercise testing. Curtis and O'Keefe write: "The status of the autonomic nervous system, although often ignored by clinicians, is a major determinant of cardiovascular health and prognosis. Any therapy that chronically activates the sympathetic nervous system and/or diminishes parasympathetic (vagal) tone will increase the risk of cardiovascular events. In contrast, therapies that tip the autonomic balance toward parasympathetic dominance and decrease sympathetic tone will improve prognosis" (Curtis & O'Keefe, 2002). Obesity, Metabolic Syndrome, diabetes, insulin resistance, glucose intolerance and chronically elevated insulin levels are all associated with increased

sympathetic tone and these conditions should be on a Chinese medicine practitioner's alert-list when it comes to prescribing a formula containing a sympathomimetic substance such as Ma Huang. In the interest of the highest degree of public safety, in countries where ephedra is still used, practitioners of Chinese medicine do not prescribe ephedra-containing formulas to patients who have any contraindications such as hypertension, heart disease, hyperthyroidism and diabetes.

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References

- Abourashed, E., El-Alfy, A., Khan, I. & Walker, L. (Aug 2003). "Ephedra in Perspective: A Current Review", *Phytother. Res.*, 17(7), 703-712
- Adamson, P., Suarez, J., Ellis, E., Kanaly, T. & Vanoli, E. (2004). "Ephedrine increases ventricular arrhythmias in conscious dogs after myocardial infarction", *J. Am. Coll. Cardiol.*, 19:44(8), 1675-1678
- Barceloux, D.G. (2008). *Medical Toxicity of Natural Substances*. John Wiley & Sons Inc.: Hoboken
- Bensky, D. & Clavey, S. (2004). *Chinese Herbal Medicine Materia Medica*. 3rd Edition. Eastland Press: Seattle
- Canale, M.P., Manca di Villahermosa, S., Martino, G., Rovella, V., De Lorenzo, A. & Di Daniele, N. (2013). "Obesity-related metabolic syndrome: mechanisms of sympathetic overactivity", *Int. J. Endocrinol.* 865965 [last accessed 08/01/2016]
- Chan, C.K., Kuo, M.L., Shen, J.J., See, L.C., Chang, H.H. & Huang, J.L. (2006). "Ding Chuan Tang, a Chinese herb decoction, could improve airway hyper-responsiveness in stabilized asthmatic children: a randomized, double-blind clinical trial", *Pediatr. Allergy Immunol.*, 17(5), 316-322
- Chang, R.S., Wang, S.D., Wang, Y.C., Lin, L.J., Kao, S.T. & Wang J.Y. (2013). "Xiao-Qing-Long-Tang shows preventive effect of asthma in an allergic asthma mouse model through neurotrophin regulation", *BMC Complement. Altern. Med.*, 8:13, 220
- Chen, H.Y., Lin, Y.H., Thien, P.F., Chang, S.C., Chen, Y.C., Lo S.S., Yang, S.H. & Chen J.L. (2013). "Identifying core herbal treatments for children with asthma: implication from a Chinese herbal medicine database in Taiwan", *Evid. Based Complement. Alternat. Med.*, 125943 [last accessed 08/01/2016]
- Chen, J.K. & Chen, T.T. (2009). *Chinese Herbal Formulas and Applications. Pharmacological Effects & Clinical Research*. Art of Medicine Press: City of Industry
- Chen, J.K. & Chen, T.T. (2012). *Chinese Medical Herbology and Pharmacology*. Art of Medicine Press: City of Industry
- Chen, K.K. & Schmidt, C.F. (1930). *Ephedrine and Related Substances*. Bailliere, Tindall & Cox: London & The Williams and Wilkins Company: Baltimore
- Chen, K.K. & Schmidt, C.F. (1959). "The action and clinical use of ephedrine, an alkaloid isolated from the Chinese drug ma huang; historical document". *Ann. Allergy*, 17, 605-18
- Chen, Z.G., Luo, H., Wang, S.C., Xu, J.Y. & Li Y.X. (2015). "Antiviral effects of Jinxin oral liquid against respiratory syncytial virus infection in the BALB/c mice model", *J. Ethnopharmacol.*, 13, 162, 287-295
- Cordain, L., Eades, M.R., Eades, M.D. (2003). "Hyperinsulinemic diseases of civilization: More than just Syndrome X", *Comp. Biochem. Physiol. A. Mol. Integr. Physiol.*, 136(1), 95-112
- Curtis, B. & O'Keefe, J. Jr. (2002). "Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight", *Mayo Clin. Proc.*, 77(1), 45-54
- Derelanko, M.J., Auletta, C.S. (2014). *Handbook of Toxicology*. 3rd Ed. CRC Press: Boca Raton, London, New York
- Drew, C., Knight, G., Hughes, D. & Bush, M. (1978). "Comparison of the effects of D(-)-ephedrine and L-(+)-pseudoephedrine on the cardiovascular and respiratory systems in man", *Br. J. Clin. Pharmacol.*, 6(3), 221-225
- Faber, M., Jetter, A. & Fuhr, U. (2005). "Assessment of CYP1A2 Activity in Clinical Practice: Why, How, and When?", *Basic & Clinical Pharmacology & Toxicology*, 97(3), 125-134
- Fairchild, M.D. & Alles, G.A. (1967). "The central locomotor stimulatory activity and acute toxicity of the ephedrine and norephedrine isomers in mice." *J Pharmacol Exp Ther.*, 158(1), 135-139.
- Feller, D. & Malspeis, L., (1977). "Biotransformation of D(-)-ephedrine and L-(+)-ephedrine in the rabbit, in vivo and in vitro", *Drug Metab. Dispos.*, 5(1), 37-46
- Haller, C.A. & Benowitz, N.L., (2000). "Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedra Alkaloids", *N. Engl. J. Med.*, 21:343(25), 1833-1838
- Haller, C.A., Duan, M., Benowitz, N.L. & Jacob, P. (2004). "Concentrations of ephedra alkaloids and caffeine in commercial dietary supplements", *J. Anal. Toxicol.*, 28(3), 145-151
- Haller, C.A., Jacob, P. & Benowitz, N.L. (2004). "Enhanced stimulant and metabolic effects of combined ephedrine and caffeine", *Clin. Pharmacol. Ther.*, 75(4), 259-273
- Haller, C.A., Jacob, P. & Benowitz, N.L. (2002). "Pharmacology of ephedra alkaloids and caffeine after single-dose dietary supplement use", *Clin. Pharmacol. Ther.*, 71(6), 421-432
- Haller, C.A., Jacob, P. & Benowitz, N.L. (2005). "Short-term metabolic and hemodynamic effects of ephedra and guarana combinations", *Clin. Pharmacol. Ther.*, 77(6), 560-571
- Hayashi, K., Imanishi, N., Kashiwayama, Y., Kawano, A., Terasawa, K., Shimada, Y. & Ochiai, H. (2007). "Inhibitory effect of cinnamaldehyde, derived from Cinnamomi cortex, on the growth of influenza A/PR/8 virus in vitro and in vivo", *Antiviral Res.*, 74(1), 1-8
- Hayashi, K., Shimura, K., Makino, T. & Mizukami, H. (2010). "Comparison of the contents of kampo decoctions containing ephedra herb when prepared simply or by re-boiling according to the traditional theory", *J. Nat. Med.*, 64(1), 70-74
- Hoffman, K.B., Demakas, A., Erdman, C.B., Dimbil, M. & Doraiswamy PM. (2013). "Neuropsychiatric adverse effects of oseltamivir in the FDA Adverse Event Reporting System 1999-2012", *B.M.J.*, 23, 347
- Hong, M.L., Song, Y. & Li, X.M. (2011). "Effects and mechanisms of actions of Chinese herbal medicines for asthma", *Chin. J. Integr. Med.*, 17(7), 483-491
- Hsieh, C.F., Lo, C.W., Liu, C.H., Lin, S., Yen, H.R., Lin, T.Y. & Horng, J.T. (2012). "Mechanism by which mao-xing-shi-gan-tang inhibits the entry of influenza virus", *J. Ethnopharmacol.*, 143(1), 57-67
- Huang, T.P., Liu, P.H., Lien, A.S., Yang, S.L., Chang, H.H. & Yen, H.R. (2013). "Characteristics of traditional Chinese medicine use in children with asthma: a nationwide population-based study", *Allergy*, 68(12), 1610-1613
- Kao, S.T., Chang, C.H., Chen, Y.S., Chiang, S.Y. & Lin, J.G. (2004). "Effects of Ding-Chuan-Tang on bronchoconstriction and airway leucocyte infiltration in sensitized guinea pigs", *Immunopharmacol. Immunotoxicol.*, 26(1), 113-124

- Kao, S.T., Wang, S.D., Wang, J.Y., Yu, C.K. & Lei, H.Y. (2000). "The effect of Chinese herbal medicine, xiao-qing-long tang (XQLT), on allergen-induced bronchial inflammation in mite-sensitized mice", *Allergy*, 55(12), 1127-1133
- Kernan, W.N., Viscoli, C.M., Brass, L.M., Broderick, J.P., Brott, T., Feldmann, E., Morgenstern, L.B., Wilterdink, J.L. & Horwitz, R.I. (2000). "Phenylpropanolamine and the risk of hemorrhagic stroke", *N. Engl. J. Med.*, 343(25), 1826-1832
- Kubo, T. & Nishimura H. (2007). "Antipyretic effect of Mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children", *Phytomedicine*, 14(2-3), 96-101
- Lambert, E.A., Straznicki, N.E., Dixon, J.B. & Lambert, G.W. (2015). "Should the sympathetic nervous system be a target to improve cardiometabolic risk in obesity?", *Am. J. Physiol. Heart Circ. Physiol.*, 309(2), 244-258
- Lee, M.R. (2011). "The history of Ephedra (ma-huang)", *J. R. Coll. Physicians Edinb.*, 41(1), 78-84
- Luo, H., Li, Q., Flower, A., Lewith, G. & Liu, J. (2012). "Comparison of effectiveness and safety between granules and decoction of Chinese herbal medicine: a systematic review of randomized clinical trials", *J. Ethnopharmacol.*, 10;140(3), 555-67
- Ma, C.H., Ma, Z.Q., Fu, Q. & Ma, S.P. (2014). "Ma Huang Tang ameliorates asthma through modulation of Th1/Th2 cytokines and inhibition of Th17 cells in ovalbumin-sensitized mice", *Chin. J. Nat. Med.*, 12(5), 361-6
- Ma, L.Q., Pan, C.S., Yang, N., Liu, Y.Y., Yan, L., Sun, K., Wei, X.H., He, K., Xiao, M.M., Fan, J.Y. & Han, J.Y. (2014). "Posttreatment with Ma-Xing-Shi-Gan-Tang, a Chinese medicine formula, ameliorates lipopolysaccharide-induced lung microvessel hyperpermeability and inflammatory reaction in rat", *Microcirculation*, 21(7), 649-663
- Mantini, N., Andoh, T., Kawamata, H., Terasawa, K. & Ochiai, H. (2007). "Inhibitory effect of Ephedrae herba, an oriental traditional medicine, on the growth of influenza A/PR/8 virus in MDCK cells", *Antiviral Res.*, 74(1), 1-8
- Mei, F., Xing, X.F., Tang, Q.F., Chen, F.L., Guo, Y., Song, S., Tan, X.M. & Luo, J.B. (2014). "Antipyretic and anti-asthmatic activities of traditional Chinese herb-pairs, Ephedra and Gypsum", *Chin. J. Integr. Med.*, Epub ahead of print [last accessed 08/01/2016]
- Ministry of Health, Labour and Welfare of Japan (2011). *Japanese Pharmacopoeia XVI*. English Ed.
- Ministry of Health, Labour and Welfare of Japan (2014). *Japanese Pharmacopoeia XVI Supplement II*. English Ed.
- Ministry of Health of the People's Republic of China (2010). 中华人民共和国药典 (Zhong Hua Ren Ming He Guo Yao Dian, Pharmacopoeia of the People's Republic of China)
- Mitchell, C., Feng, Y. & Wiseman, N. (1999). *Zhang Zhong-Jing's Shang Han Lun: On Cold Damage. Translation and Commentary*. Paradigm Publications: Brookline
- Morgenstern, L.B., Viscoli, C.M., Kernan, W.N., Brass, L.M., Broderick, J.P., Feldmann, E., Wilterdink, J.L., Brott, T. & Horwitz, R.I. (2003). "Use of Ephedra-containing products and risk for hemorrhagic stroke", *Neurology*, 60, 132-135
- National Institute of Health, National Center for Complementary and Integrative Health (2006). *Ephedra Fact Sheet*, available at <https://nccih.nih.gov/health/ephedra> [last accessed 16.01.2016]
- Nabeshima, S., Kashiwagi, K., Ajisaka, K., Masui, S., Takeoka, H., Ikematsu H. & Kashiwagi, S. (2012). "A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza", *Journal of Infection and Chemotherapy*, 18(4), 534-543
- Nagai, T., Kataoka, E., Aoki, Y., Hokari, R., Kiyohara, H. & Yamada H. (2014). "Alleviative Effects of a Kampo (a Japanese Herbal) Medicine "Maoto (Ma-Huang-Tang) " on the Early Phase of Influenza Virus Infection and Its Possible Mode of Action", *Evid. Based Complement Alternat. Med.*, 187036 [last accessed 08/01/2016]
- Nagai, T., Urata, M. & Yamada, H. (1996). "In vivo anti-influenza virus activity of Kampo (Japanese herbal) medicine "Sho-seiryu-to"--effects on aged mice, against subtypes of a viruses and B virus, and therapeutic effect", *Immunopharmacol. Immunotoxicol.*, 18(2), 193-208
- Nakao, M., Muramoto, Y., Hisadome, M., Yamano, N., Shoji, M., Fukushima, Y., Saruwatari, J. & Nakagawa, K. (2007). "The effect of Shoseiryuto, a traditional Japanese medicine, on cytochrome P450s, N-acetyltransferase 2 and xanthine oxidase, in extensive or intermediate metabolizers of CYP2D6", *Eur. J. Clin. Pharmacol.*, 63(4), 345-353
- Nebert, D. & McKinnon, R. (1994). "Cytochrome P450: evolution and functional diversity", *Prog. Liver Dis.*, 12, 63-97
- Neff, G.W., Reddy, K., Durazo, F., Meyer, D., Marrero, R. & Kaplowitz, N. (2004). "Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid", *J. Hepatol.*, 41(6), 1062-1064
- Ohara, K., Oshima, S., Fukuda, N., Ochiai, Y., Maruyama, A., Kanamuru, A., Negishi, A., Honma, S., Ohshima, S., Akimoto, M., Takenaka, S. & Kobayashi, D. (2015). "The inhibitory effect of kakkonto, Japanese traditional (kampo) medicine, on brain penetration of oseltamivir carboxylate in mice with reduced blood-brain barrier function", *Evid Based Complement Alternat Med.*, 917670 [last accessed 08/01/2016]
- Persky, A., Berry, N., Pollack, G. & Brouwer, K. (2004). "Modelling the cardiovascular effects of ephedrine", *Br. J. Clin. Pharmacol.*, 57(5), 552-62
- Relling, M., Lin, J., Ayers, G. & Evans, W. (1992). "Racial and gender differences in N-acetyltransferase, xanthine oxidase, and CYP1A2 activities", *Clin. Pharmacol. Ther.*, 52(6), 643-658
- Robertson, D., Frolich, J., Carr, R.K., Watson, T., Hollifield, J., Shand, D. & Oates, J. (1978). "Effects of Caffeine on Plasma Renin Activity, Catecholamines and Blood Pressure", *N. Engl. J. Med.*, 26;298(4), 181-186
- Sagliani, S. & Lloyd, C.M. (2014). "Eosinophils in the pathogenesis of paediatric severe asthma", *Curr. Opin. Allergy Clin. Immunol.*, 14(2), 143-8
- Samenuk, D., Link, M., Homoud, M., Contreras, R., Theoharides, T., Wang, P. & Estes, N. (2002). "Adverse Cardiovascular Events Temporally Associated with Ma Huang, an Herbal Source of Ephedrine", *Mayo Clin. Proc.*, 77(1), 12-16
- Schlaich, M., Straznicki, N., Lambert, E. & Lambert, G. (2015). "Metabolic syndrome: a sympathetic disease?", *Lancet Diabetes Endocrinol.*, 3(2), 148-57
- Sever, P., Dring, L. & Williams R. (1975). "The metabolism of (-) ephedrine in man", *Eur. J. Clin. Pharmacol.*, 19;9(2-3), 193-198
- Shekelle, P., Hardy, M., Morton, C., Maglione, M., Mojica, W., Sutton, M., Rhodes, S., Jungvig, L. & Gagne J. (2003). "Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis", *JAMA.*, 26;289(12), 1537-1545
- Song, S., Chen, F., Xing, X., Ren, M., Ma, Q., Xie, Y., Tang, Q. & Luo, J. (2015). "Concurrent quantification and comparative pharmacokinetic analysis of bioactive compounds in the Herba Ephedrae-Semen Armeniacae Amarum herb pair", *J. Pharm. Biomed. Anal.*, 10;109, 67-73
- Tang, J., Zhou, X., Ji H., Zhu, D. & Wu, L. (2012). "Effects of ephedra water decoction and cough tablets containing ephedra and liquorice on CYP1A2 and the pharmacokinetics of theophylline in rats", *Phytother Res.*, 26(3), 470-474
- Tao, H.J. (ca.494). Collection of Commentaries on the Classic of the Materia Medica (Shen Nong Ben Cao Jing Ji Zhu, 神農本草經集注), available at <http://www.zysj.com.cn/lilunshuji/bencaojingjizhu5325/> [accessed 07.01.2016]
- Thorp, A., Schlaich, M. (2015). "Relevance of Sympathetic Nervous System Activation in Obesity and Metabolic Syndrome", *J. Diabetes Res.*, 341583
- Toriumi, Y., Kamei, T., Murata, K., Takahashi, I., Suzuki, N. & Mazda, O. (2012). "Utility of Maotoinan influenza season where reduced effectiveness of oseltamivir was observed - a clinical non-randomized study in children," *Forsch. Komplementmed.*, 19(4), 179-186
- Unschuld, P. (2003). *Huang Di Nei Jing Suwen: Nature, Knowledge, Imagery in an Ancient Chinese Medical Text*. University of California Press: London
- Wang, H.M., Lin, S.K., Yeh, C.H. & Lai, J.N. (2014). "Prescription pattern of Chinese herbal products for adult-onset asthma in Taiwan: a population-based study", *Ann. Allergy Asthma Immunol.*, 112(5), 465-470
- Wang, S.D., Lin, L.J., Chen, C.L., Lee, S.C., Lin, C.C., Wang, Y.J. & Kao, S.T. (2012). "Xiao-Qing-Long-Tang attenuates allergic airway inflammation and remodeling in repetitive Dermatogoides pteronyssinus challenged chronic asthmatic mice model", *J. Ethnopharmacol.*, 142(2), 531-538
- Watson, R., Woodman, R. & Lockette, W. (2010). "Ephedra alkaloids inhibit platelet aggregation", *Blood Coagul. Fibrinolysis*, 21(3), 266-271
- White, L., Gardner, S., Gurley, B., Marx, M., Wang, P. & Estes, M. (1997). "Pharmacokinetics and cardiovascular effects of ma-huang (Ephedra sinica) in normotensive adults", *J. Clin. Pharmacol.*, 37(2), 116-122
- Wiseman, N. & Feng, Y. (1998). *A Practical Dictionary of Chinese Medicine*. 2nd Edition. Paradigm Publications: Brookline
- Yamada, H. & Nagai, T. (1998). "In vivo antiinfluenza virus activity of Kampo medicine Sho-seiryu-to through mucosal immune system", *Methods Find. Exp. Clin. Pharmacol.*, 20(3), 185-192
- Yang, S. (2012). *The Divine Farmer's Materia Medica: A Translation of the Shen Nong Ben Cao Jing by Yang Shou-zhong*. Blue Poppy Press: Boulder
- Yu, F., Takahashi, T., Moriya, J., Kawaura, K., Yamakawa, J., Kusaka, K., Itoh, T., Morimoto, S., Yamaguchi, N. & Kanda T. (2006). "Traditional Chinese medicine and Kampo: a review from the distant past for the future", *J. Int. Med. Res.*, 34(3), 231-239
- Yuan, D., Komatsu, K., Cui, Z. & Kano, Y. (1999). "Pharmacological properties of traditional medicines (XXV). Effects of ephedrine, amygdalin, glycyrrhizin, gypsum and their combinations on body temperature and body fluid", *Biol. Pharm. Bull.*, 22(2), 165-171
- Yuan, D., Komatsu, K., Tani, H., Cui, Z. & Kano, Y. (1998). "Pharmacological properties of traditional medicines. XXIV. Classification of antiasthmatics based on constitutional predispositions", *Biol. Pharm. Bull.*, 21(11), 1169-1173
- Yuan, D., Sunouchi, H., Sakurai, T., Saito, K. & Kano, Y. (2002). "Pharmacological properties of traditional medicines (XXVII). Interaction between Ephedra Herb and Gypsum under hyperthermal conditions in rats", *Biol. Pharm. Bull.*, 25(7), 872-874
- Zheng, F.H., Wei, P., Huo, H.L., Xing, X.F., Chen, F.L., Tan, X.M. & Luo J.B. (2015). "Neuroprotective effect of gui zhi (ramulus cinnamomi) on ma huang- (herb ephedra-) induced toxicity in rats treated with a ma huang-gui zhi herb pair", *Evid. Based Complement. Alternat. Med.*, 913461 [last accessed 08/01/2016]
- Zhu, Y. (1998). *Chinese Materia Medica: Chemistry, Pharmacology and Applications*. CRC Press: Boca Raton, London, New York