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REVIEW ARTICLE

Ephedra in Perspective – a Current Review

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Although the traditional use of Ephedra 'ma huang' has been established for thousands of years, its resurgence in the US as a herbal dietary supplement is currently a matter of national controversy. At the heart of the debate are three important questions: (1) the identity and composition of Ephedra products with regard to ephedrine and related alkaloids; (2) the potential therapeutic utility of Ephedra supplements for weight loss or performance enhancement; and (3) potential health risks associated with such uses of Ephedra, particularly in sensitive individuals or in cases of intentional abuse for its stimulant properties. This review surveys the literature on Ephedra with regard to traditional uses, botany, chemistry, analytics, pharmacological effects and health risks. A brief discussion of the central issues in the current debate on the regulation of Ephedra in the United States is included as this is where most of the problems have occurred to date. Copyright © 2003 John Wiley & Sons, Ltd.

Keywords: Ephedra; ma huang; chemistry; pharmacology; regulation; dietary supplements; review.

INTRODUCTION

One of the oldest medicinal herbs known to mankind is probably Ephedra, or ma huang as it is known in Traditional Chinese Medicine (TCM). A member of family Ephedraceae, *Ephedra sinica* is the primary species that has been used in China for more than 5000 years and is still being used in Ephedra preparations and extracts all around the world (Chen and Schmidt, 1926; Weiss, 1988). Although originally examined by Emperor Shen Nung (ca. 3200 BC), the use of ma huang as a stimulant and as an antiasthmatic was not documented until the time of the ancient Chinese Han Dynasty (ca. 207 BC–220 AD) (Chen and Schmidt, 1926; Bensky and Gamble, 1993). *Ephedra gerardiana* has been similarly employed in Indian folk medicine since old times. Even during the time of the Roman Empire, Ephedra was well known and described until it was eventually dropped from medieval European literature (Jones, 1999). More recently, the importance of some Ephedra species as potential cash crops in India and the United States has been contemplated (Morton, 1977; Jones, 1999). In spite of its long history and its agronomic promise, the use of Ephedra herb has declined throughout the years, but in the beginning of the 20th century, interest in the herb gradually revived, as demonstrated by its use in the US for weight loss and performance enhancement. Over the past decade, however, the use of Ephedra in the US has been under increasing scrutiny due to the mounting evidence of possible hazards caused by misuse or abuse of the herb.

The goal of this review is to provide an overview of the scientific facts, clinical findings and the current legal issues about the Ephedra herb and to touch on the prospects of its future utilization in traditional medicine and in the herbals industry.

BOTANY

The Family Ephedraceae includes ca. 45 species of the genus *Ephedra* indigenous to the temperate and subtropical regions of Asia, Europe, North and Central America. The plants are herbaceous perennials that can exceed 1 m in height, with a strong pine odor and an astringent taste (Morton, 1977; Leung and Foster, 1996). The Chinese term '*ma huang*' may be loosely translated as 'yellow astringent', 'yellow horsetail' or 'hemp yellow' (*huang* is yellow; *ma* has different meanings) and is more specific to the aerial parts of *Ephedra sinica* Stapf., *E. equisietina* Bunge., or *E. intermedia* Schrenk et Mey (Bensky and Gamble, 1993). Other species that are not official in the Chinese Pharmacopoeia but that are also considered as sources of ma huang include *E. minuta* Florin, *E. distachya* L. and *E. gerardiana* Wall., as well as at least 6 more ephedrine-containing species (Leung, 1999). Although China has been the main supplier of the herb, India and Pakistan are currently accepted as major suppliers as well (Samuelsson, 1992). The organs used in traditional medicine are the dried green stems, which are usually boiled in water and administered as a hot tea. The usual daily dose is 1.5–9 g of the decocted herb (Leung, 1999).

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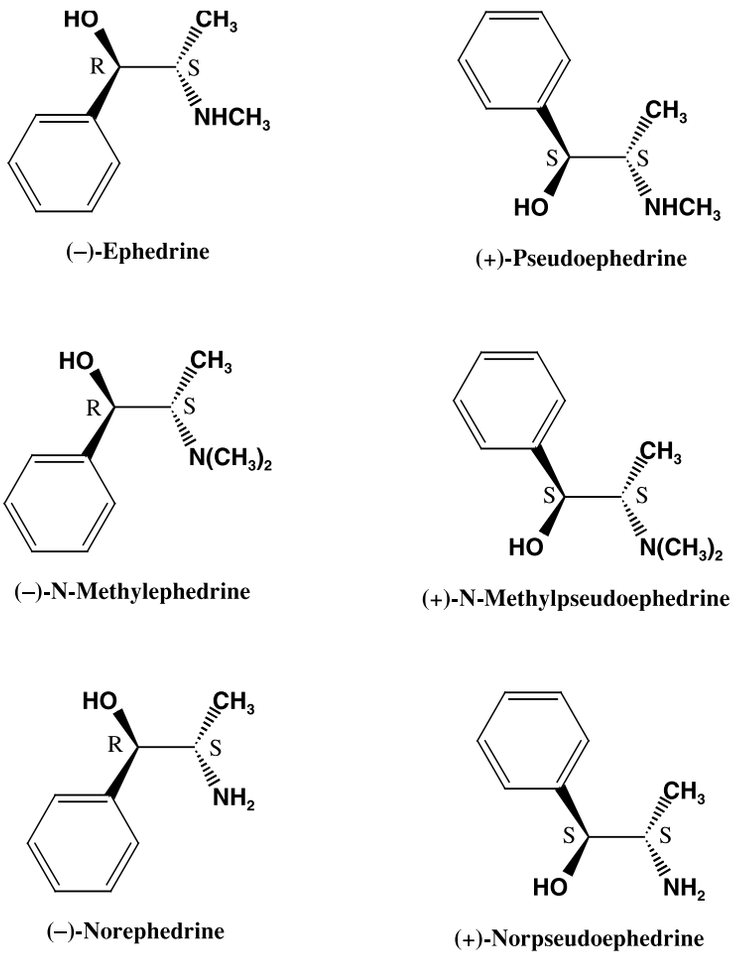


Figure 1. Naturally Occurring Ephedra Alkaloids.

CHEMISTRY

The aerial parts of different *Ephedra* species contain from 0.02% to 3.4% of 6 optically active alkaloids (Fig. 1) concentrated in the internodes (Leung and Foster, 1996). (–)-Ephedrine (EPH) is the major isomer comprising 30–90% of the total alkaloids. It was the first alkaloid isolated from *Ephedra* by Nagai in 1887. (+)-Pseudoephedrine (PSE), the diastereomer of (–)-EPH, was subsequently isolated by Ladenburg and Ölschlägel in 1889 followed by the remaining isomers in the late 1920s. A minor bioactive oxazolidone derivative of (–)-EPH, ephedroxane, has also been isolated from the aerial parts of *E. intermedia* and has been detected in at least 6 more species containing ephedrine alkaloids (Konno *et al.*, 1979). The biosynthetic pathway to Ephedra alkaloids has been established to be through the condensation of a C_6–C_1 benzoic acid unit, originating from phenylalanine, with an intact CH_3CO group derived from pyruvic acid (Grue-Sorensen and Spenser, 1993). Preparation of Ephedra alkaloids from crude plant material involves the acid/base extraction procedure presented in Fig. 2. Alternatively, numerous methods for obtaining such alkaloids via chemical synthesis have been published. Most of these methods, however, result in racemic mixtures of the alkaloids and only a few, based on asymmetric synthesis, provide the optically active isomers. The most economical and popular method for large scale production of

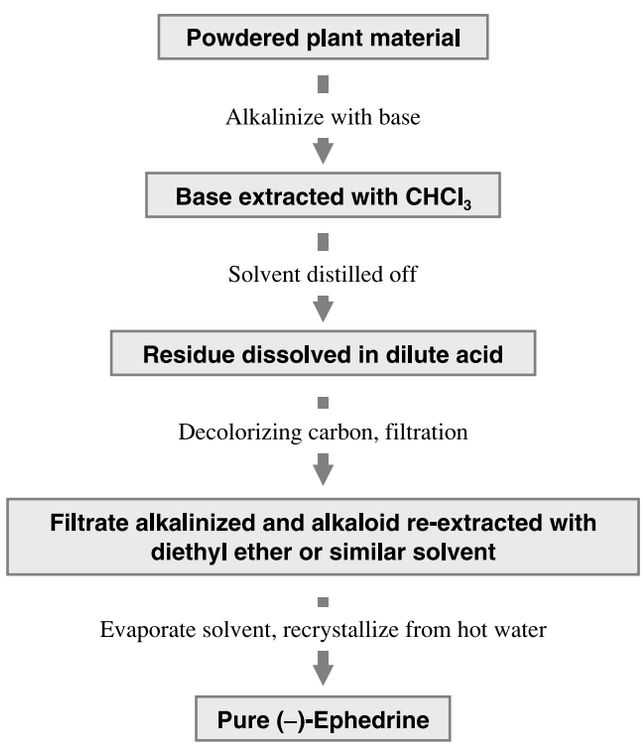


Figure 2. Preparation of (–)-ephedrine from crude ma huang (Reti 1953).

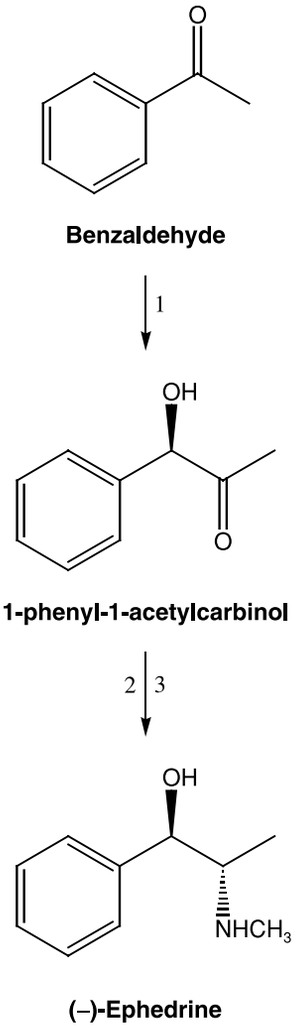


Figure 3. Asymmetric synthesis of (–)-ephedrine (Hutchinson and Andrews, 1995). 1. molasses fermentation; 2. CH_3NH_2; 3. H_2/Pt.

pharmaceutical (–)-EPH is through the fermentation of a mixture of benzaldehyde and molasses followed by reductive amination of the resulting carbinol (Fig. 3) (Neuberg and Hirsch, 1921; Hutchinson and Andrews, 1995). The resulting (–)-EPH is recrystallized as the HCl salt. (+)-PSE is subsequently produced from (-)-EPH HCl via an acetylation/deacetylation procedure. It is to be noted that not all *Ephedra* species contain ephedrine-type alkaloids. *Ephedra nevadensis*, known as Mormon or desert tea, *E. trifurca*, and *E. antisyphilitica*, as well as most North and Central American species are believed to be devoid of these alkaloids (Tyler, 1999).

In addition to the ephedrine-type alkaloids, other alkaloids and amino compounds have been isolated from different species of *Ephedra* (Table 1). The macrocyclic spermine alkaloids, Ephedradines A-D have been isolated from the roots *E. sinica*. Kynurenic acid derivatives have been found in the fresh stem extracts of *E. foeminea* and *E. foliata*. The fresh stems of *E. foeminea* and *E. altissima* have been reported to contain cyclopropylglycine and methanoproline amino acids. Different types of secondary metabolites, such as flavones (Taraskina *et al.*, 1966; Taraskina and Chumbalov, 1970; Castledina and Harborne, 1976; Chumbalov and Chekmeneva, 1976), flavanols, tannins (Taraskina and Chumbalov, 1970), carboxylic acids and volatile terpenes have also been reported (Table 2).

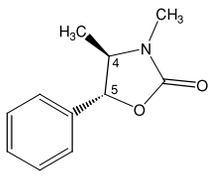
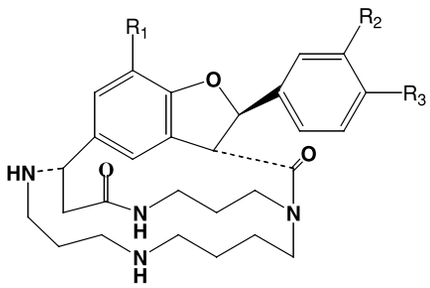
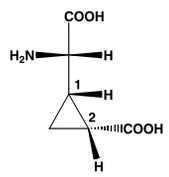
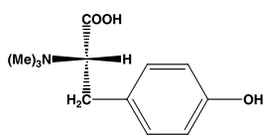
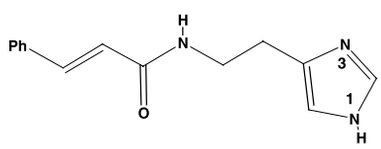
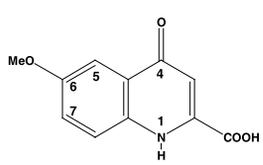
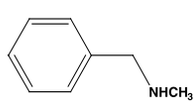
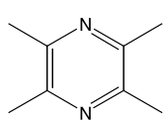
PHARMACOLOGY, TOXICOLOGY AND THERAPEUTICS

The pharmacology of Ephedra is complex, but for both traditional and more recent popular uses, the established pharmacological effects appear to be attributable to its ephedrine-type alkaloids, mainly (–)-EPH and (+)-PSE. Pharmacological studies of Ephedra began shortly after ephedrine was first isolated and were focused on the pure compound rather than on the whole herb extract (Takahashi and Miura, 1888). The other natural isomers of ephedrine were subsequently utilized in studies conducted around the turn of the century in China and Japan (Amatsu and Kubota 1917; Chen and Schmidt, 1926). It was not until the 1920s that the pharmacological study of Ephedra alkaloids has been introduced in Western literature. Current Western therapies utilize these two alkaloids (and until recently norephedrine, also known as phenylpropanolamine) in their optically pure forms or as their synthetic racemates. Due to their stability, they are often incorporated in oral dosage forms. This review of Ephedra pharmacology treats first the investigations of the individual alkaloids.

Ephedrine is a sympathomimetic agonist at both α- and β-adrenergic receptors. It also displays indirect sympathetic activation, in that it enhances the release of norepinephrine from sympathetic neurons. This basic pharmacological mechanism seems to account for most of ephedrine's therapeutic efficacy, as well as its most prominent adverse effects. Hallmark effects of α- and β-adrenergic receptor stimulation include enhanced cardiac rate and contractility, peripheral vasoconstriction, bronchodilation, and central nervous system (CNS) stimulation. The vasoconstrictor and bronchodilator effects explain the traditional use of Ephedra as a nasal decongestant and anti-asthmatic. Ephedrine is metabolized to norephedrine (phenylpropanolamine) which may be responsible for the CNS stimulant effects (Dollery, 1991). In current usage, the CNS stimulant and perhaps thermogenic effects are purported to afford enhanced weight loss in obesity, and improved performance in endurance training or body-building. Although ephedrine does suppress appetite, the main mechanism for promoting weight loss appears to be by increasing the metabolic rate of adipose tissue (Murray, 1995). In view of the established pharmacological activities, ephedrine administration is contraindicated in patients with hypertension or other cardiovascular diseases, glaucoma, diabetes and hyperthyroidism (Fetrow and Avila, 1999; Tyler, 1999). These and other pharmacological and toxicological aspects of the sympathomimetic actions of ephedrine are summarized in Table 3.

The actions of ephedrine and its congeners as sympathomimetics have been studied extensively, but variations in the compounds tested, species, target tissue, and study conditions vary sharply. It can generally be concluded that ephedrine shows relatively nonselective α, β1 and β2 effects, and these may relate in part to its norepinephrine-releasing actions. Vansal and

Table 1. Non-ephedrine alkaloids and amino compounds in *Ephedra* species

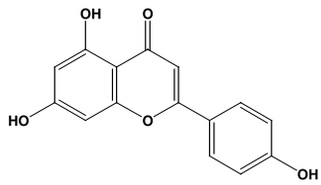
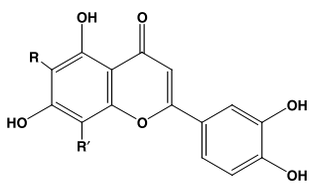
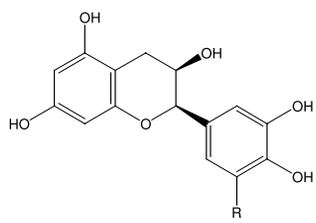
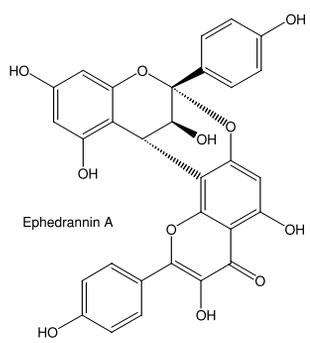
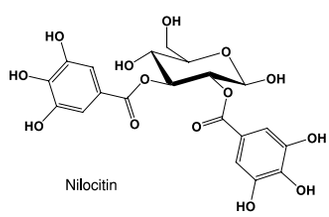
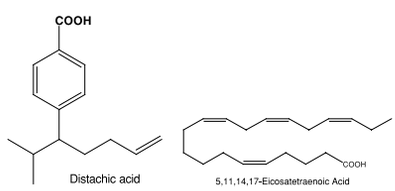
Compound Name	Chemical Structure	Source/Organ	Reference
Ephedroxane		Aerial parts of *Ephedra* herb	(Konno *et al.*, 1979)
Ephedradine A, $R_1 = R_2 = R_3 = H$ Ephedradine B, $R_1 = R_3 = H$, $R_2 = OMe$ Ephedradine C, $R_1 = H$, $R_2 = OMe$, $R_3 = Me$ Ephedradine D, $R_1 = OMe$, $R_2 = R_3 = H$		Aerial parts of *Ephedra* herb	(Tamada *et al.*, 1979, Hikino *et al.*, 1983b)
Cyclopropyl-α-amino acids		Stems of *E. altissima* *E. foeminea*	(Starrat and Caveney, 1995)
Maokonine		*Ephedra* root	(Tamada *et al.*, 1978)
Feruloylhistamine		*Ephedra* root	(Hikino *et al.*, 1983a, Hikino *et al.*, 1984)
6-Methoxykynurenic acid		Fresh stem of *E. pachyclada*	(Nawwar *et al.*, 1985, Starrat and Caveney, 1996)
N-methylbenzylamine		Ephedra herb	(Chen *et al.*, 1931)
Tetramethylpyrazine		Ephedra herb	(Leung and Foster, 1996)

Feller examined the direct effects of four ephedrine isomers on human β-adrenergic receptors (β-AR), including the β_3-subtype involved in lipolysis and non-shivering thermogenesis. Results demonstrated that all isomers exerted different effects on all receptors and that (–)-EPH was the most potent and the only isomer to possess a weak partial agonist activity on β_3-AR (Vansal and Feller, 1999).

On the other hand, the most popular application of pseudoephedrine is in flu medications to relieve nasal decongestion due to its vasoconstrictive (Hoffman and Lefkowitz, 1996) and perhaps an anti-inflammatory effect (Hikino *et al.*, 1980).

In addition to the ephedrine alkaloids, some of the minor compounds isolated from *Ephedra* species exhibited other biological activities. Ephedroxane, was

Table 2. Miscellaneous Non-alkaloidal Natural Constituents of Ephedra

Compound Class	Chemical Structure and name	Source	Reference
Flavones	 Apigenin	*E. antisyphylitica*	(Taraskina *et al.*, 1966, Taraskina and Chumbalov, 1970, Castledina and Harborne, 1976, Chumbalov and Chekmeneva, 1976)
	 Lucenin 1, R = xyl, R′ = glu Lucenin 3, R = glu, R′= xyl		
Flavanols (Tannin precursors)	 Catechin, R = H Gallocatechin, R = OH	Twigs and barks of *E. helvetica*	(Friedrich and Wiedemeyer, 1976)
Bisflavanols	 Ephedrannin A	*E. sp.*	(Hikino, 1982, Bilia *et al.*, 1996)
Carboxylic Acids	 Nilocitin	*E. alata*	(Nawwar *et al.*, 1985)
	 Distachic acid 5,11,14,17-Eicosatetraenoic Acid	*E. sp.*	(Takagi and Itabashi, 1982, Song, 1994)

found to have anti-inflammatory activity (Konno *et al.*, 1979; Kasahara *et al.*, 1985); while others, such as Ephedrannine A and maokonine exhibited hypotensive activity in animals (Tamada *et al.*, 1978). It is interesting to notice that the reported hypotensive activity is exhibited by compounds present only in the roots of Ephedra, which agrees with Chinese belief that the roots constitute a drug (ma huang gen, or mao-kon in Japanese) that produces opposite effects to those of the aerial parts (ma huang). The former observation is not contradicted by the fact that, maokonine, an L-tyrosine betaine isolated from the roots, exhibits hypertensive activity comparable with the action of ephedrine, since the overall effect of the root extract is still hypotensive in nature (Tamada *et al.*, 1978).

The hypoglycemic effect of *E. distachya* has been investigated in Japan to show that the hydroalcoholic extract produced long lasting hypoglycemia in mice following transient hyperglycemia. Activity-guided fractionation resulted in the isolation of five active glycans,

Table 3. Pharmacology, therapeutics and toxicity of ephedrine (Hoffman and Lefkowitz, 1996)

Pharmacol. Effect	Therapeutic Use	Side Effect	Toxicity
Increase in heart rate Elevation of blood pressure	Specific cases of heart block, postural hypotension and hypotension associated with spinal anesthesia	Hypertension, palpitations	Arrhythmias Myocardial infarction Stroke Cardiac arrest Death
Constriction of peripheral blood vessels	Local antihistamines	Dry exfoliating skin	
Bronchodilation	Bronchial asthma		
Mydriasis		Dizziness	
CNS stimulation	Narcolepsy; depression	Insomnia, anxiety	Psychosis
Urine retention	Urinary incontinence	Urine retention	

Ephedrans A, B, C, D and E which significantly reduced blood glucose levels in normal and alloxan-induced diabetic mice (Konno *et al.*, 1985). In a similar investigation of the hypoglycemic activity of selected plants growing in Egypt, the alcoholic extract of *E. alata* exhibited a persistent lowering of blood glucose one hour after administration to fasting rats. In alloxanized rats, however, the same extract failed to reduce blood glucose levels as compared to the positive control, glibenclamide (Shabana, 1990). The role of Ephedra in the antitussive/antiasthmatic effect of a Japanese Kampo prescription containing 3 additional herbs was the subject of another investigation. Results from experiments conducted on guinea pigs showed that removal of Ephedra from the herbal combination of the prescription rendered it completely ineffective. Similar results were obtained in dogs to the effect that the presence of the complimentary herbs enhanced the antitussive effect of Ephedra (Hosoya, 1985). The potential use of *E. sinica* as a therapy for inflammatory diseases has been the focus of a recent study. The aqueous extract yielded a fraction rich in an uncharacterized polyanionic carbohydrate that exhibited complement-inhibiting properties in animal as well as human sera. Oral administration in rats also caused a partial inhibition of serum complement activity. The reported findings may offer partial support for the TCM use of *E. sinica* in acute nephritis (Ling *et al.*, 1995).

On the herbal/dietary supplement frontier, ma huang has traditionally been used in China for bronchial asthma, coughs, colds, flu, fever, chills, headaches, edema, nasal congestion, and arthralgias. In the West, Ephedra preparations have been used, alone or with caffeine, as CNS stimulants and mood enhancers. Moreover, new uses for Ephedra have recently emerged. Many Ephedra-containing products are claimed to be effective for weight-loss, as energy/performance boosters, euphorics or aphrodisiacs, claims that are especially appealing to young adults (Josefson, 1995). Such claims, however, have not been adequately substantiated and, in an attempt to probe their validity, Vallerand investigated the role of EPH in thermogenesis and cold tolerance in humans. The study demonstrated that combinations of ephedrine with caffeine and/or theophylline were very effective in enhancing cold thermogenesis and delaying the onset of hypothermia. Such an effect was mainly attributed to an increase in the sympathomimetic tone resulting in increased lipolysis and glycogenolysis, with sympathetic stimulation of central satiety centers leading to appetite suppression (Vallerand, 1993). Moreover, the results of a recent randomized, double-blind trial of a herbal supplement containing Ephedra and guarana showed that the mixture effectively promoted short-term weight and fat loss in overweight humans (Boozer *et al.*, 2001). Long-term safety, however, was not investigated.

HEALTH RISKS

Many cases of serious adverse effects and even fatalities have been reported that were linked with Ephedra or ephedrine administration over the last ten years (Josefson, 1995; Zaacks *et al.*, 1999; Haller and Benowitz, 2000). Haller and Benowitz published a review of 140 reports of adverse events related to the use of dietary supplements containing Ephedra alkaloids that were submitted to the FDA between 1 June 1997, and 31 March 1999. Using a standardized rating system for assessing causation, 31% of the cases were considered to be definitely or probably related to the use of Ephedra alkaloid-containing supplements, and another 31% were deemed to be possibly related. Among these adverse events, 47% involved cardiovascular symptoms and 18% involved the central nervous system. Hypertension was the most frequent adverse effect (17 reports), followed by palpitations, tachycardia, or both (13), stroke (10), and seizures (7). Ten events led to death, and 13 cases produced permanent disability (Haller and Benowitz, 2000). Also, by the year 2000, the Food and Drug Administration (FDA) had received more than 1000 injury reports related to use of Ephedra products (Carey, 2000). With the assumption that such reports have been adequately substantiated, the causes can be attributed to at least one of the following practices linked to Ephedra:

(1) *Misuse*: [administration of overdoses of Ephedra/ephedrine-containing products in an attempt to achieve better or faster response for the desired effect]. Overdosing may also result from regular administration of Ephedra products spiked with ephedrine alkaloid(s). Even at sub-toxic levels,

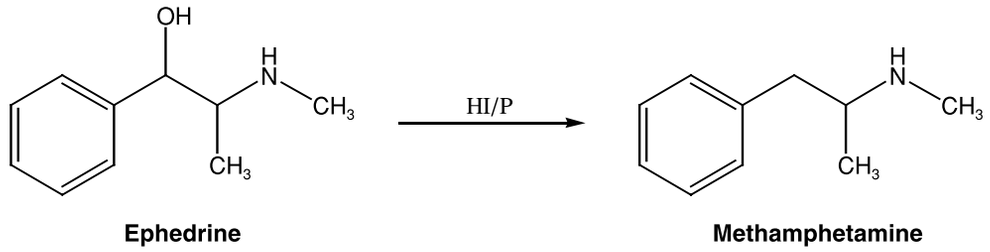


Figure 4. Synthesis of methamphetamine from ephedrine (Skinner, 1990).

spiked products may result in alkaloid levels deemed illegal in many sporting events, as was the case with a Dutch professional cyclist whose urine analysis was found positive for norpseudoephedrine at a doping control. Subsequent thorough analysis of the product proved that it had been spiked with norpseudoephedrine (Ros *et al.*, 1999).

(2) *Abuse*: [the use of illicit amphetamine derivatives (e.g. methylenedioxymethamphetamine MDMA) chemically synthesized from ephedrine and used in illegal preparations or to spike Ephedra products]. The conversion is relatively simple (Fig. 4), cheap and high yielding.

(3) *Contraindication, hypersensitivity and/or drug interaction*: [natural hypersensitivity to the pharmacological effects of Ephedra alkaloids, or possible conditions in which Ephedra administration may lead to serious side effects]. The unsupervised preoperative use of Ephedra poses a risk to patients who are later anesthesized with halothane since the later sensitizes the myocardium to ventricular arrythmias caused by exogenous catecholamines (Ang-Lee *et al.*, 2001). Moreover, the concomittent use of Ephedra with such drugs as antihypertensives or antidepressants may have a drastic influence on their intended effects.

In view of the outlined information, it becomes clear why Ephedra has arrived at its precarious situation in contrast to most other herbal supplements. It is mainly due to the specific nature of the pharmacological effects of Ephedra alkaloids, aggravated by misuse and/or abuse that the damage has been so obvious and the reaction so intense.

Other risks associated with herbal products in general may apply to Ephedra, including problems of misidentification or adulteration with other toxic plants.

A recent report described an anecdotal case of acute hepatitis associated with the use of ma-huang. A 33-year-old woman developed nausea, vomiting and jaundice for three weeks after taking a Chinese product containing ma-huang. Based on the lack of literature reports of related effects of ma-huang and ephedrine, the authors speculated that their patient must have used a ma-huang product which was misidentified, contaminated or contained some additional ingredients (Nadir *et al.*, 1996).

ANALYSIS/QUALITY CONTROL

Traditional methods for detection and quantification of Ephedra alkaloids (e.g. colorimetry, gravimetry, and titration) in various types of matrices were reported during the first half of the 20th century (Welsh, 1947). During the second half, chromatographic analytical methods gradually replaced the older ones. New separation techniques based on reversed-phase, chiral materials, ion exchange resins and capillary columns were introduced. These were coupled with various methods of detection, such as NMR spectrometry, UV spectrometry and indirect conductometry, and were efficiently controlled by computer software/hardware, which had a great impact on the currently available analytical capabilities. With the advantages of higher sensitivity, selectivity, speed and reproducibility, modern methods are well-suited for the present challenges of detecting Ephedra alkaloids and/or related illicit substances in biological fluids and in complex herbal extracts. The use of modern analytical methods in the latter case is essential for ensuring the quality, efficacy and safety of the numerous ephedrine-containing dietary supplements currently available in the market. Table 4 summarizes the most prominent analytical methods reported to date for the analysis of Ephedra alkaloids in various matrices.

Even with the current state-of-the-art, the GC and CE methods applied for the analysis of Ephedra-containing supplements are relatively slow, with elution times exceeding 40 min. A faster validated reversed-phase HPLC method has been developed for the determination of EPH, methylephedrine (MEPH), norephedrine (NEPH), norpseudoephedrine (NPSE) and PSE in dietary supplements containing *Ephedra sinica* (Gurley *et al.*, 1998). Satisfactory resolution of all five alkaloids was achieved in 21 min with retention times of 15.5, 16.3, 17.3, 18.5, and 20.9 min for EPH, MEPH, NPSE, NEPH, and PSE, respectively. Alkaloids were detected at 208 nm and the limit of quantification was 6.25 μg/ml. Another reversed-phase HPLC method, utilizing stable-isotope-labeled ephedrine as internal standard and MS detection, was also used by an FDA team for the determination of ephedrine-type alkaloids in dietary supplements. Although the method was relatively fast (25 min per analytical run), it required pre-column derivatization for sample preparation and the isocratic elution resulted in obvious tailing in slower peaks (Gay *et al.*, 2001).

Finally, a fast GC-MS method has recently been published whereby Ephedra alkaloids and 2,3,5,6-tetramethylpyrazine have been detected at nano gram levels in *E. sinica* purchased in China. The method did not require sample pretreatment and the whole analytical run did not exceed 20 min (Li *et al.*, 2001). This is of particular importance for the quality control of Ephedra products which, like many other herbal dietary supplements, often display a marked variation between manufacturer label claims versus the actual

Table 4. Different methods of analysis of Ephedra alkaloids in pharmaceuticals, biological fluids and herb

Method	Sample type	Column/Detection	Reference
HPLC	-Ephedra herbal products	C-18/UV	(Gurley *et al.*, 1998)
	-Ephedra dietary supplements	Phenyl derivative/MS	(Gay *et al.*, 2001)
	-Illicit amphetamine tablets	base-deactivated C-18/UV	(Sagara *et al.*, 1983; Longo *et al.*, 1994)
	-Cough-cold syrups	CN/conductometry	(Lau and Mok, 1995)
GC	-Urine samples (amphetamine-positive)	DB-1/NPD	(DePace *et al.*, 1990)
	-Alkaloid mixtures	DB-5/MS None/NMR	(LeBelle *et al.*, 1995)
	-Diastereomeric mixtures (carbon disulfide derivatives)	Phenelmethyl silicone/MS	(van der Merwe and Hendrikz, 1995)
	-Ephedra herbal products	Chiral (cyclodextrin)/MS	(Betz *et al.*, 1997)
CE	-Chinese herbal preparations	Uncoated capillary/UV	(Liu and Sheu 1993; Liu *et al.*, 1993)
Polarimetry	-Enantiomeric mixtures	None/polarimetry	(Engle *et al.*, 1994)
GC/MS	-Ephedra extracts	Phenylmethyl siloxane/MS	(Li *et al.*, 2001)

measured levels of the marker compounds. A demonstration of such a situation is apparent in the results of a study that utilized one of the abovementioned methods to show that the total alkaloid content in 24 Ephedra products ranged from 17–154% of the label claims (Gurley *et al.*, 2000).

REGULATION/LEGISLATION

The aforementioned concerns regarding misuse, abuse and overall safety of ma huang preparations sold as dietary supplements in the US resulted in a series of legal actions that aimed at regulating the use and propagation of the herb and its alkaloids. A chronology of such actions is listed in Table 5. During a House Government Reform Committee hearing on supplement regulation held in March 2001, many points of concern were raised about ephedra. Among such issues were unsubstantiated indications in weight loss and energy boosting; the misleading use of 'energy booster' *vs* 'stimulant' in relation to calorie intake and consumption; the amount of Ephedra permitted per dose per day; and the ability of the FDA to remove Ephedra from the market, if deemed necessary. The role of regulations in aggravating the current situation was also debated (2001). Meanwhile, a number of supplement companies are facing consumer and personal injury lawsuits related to their ephedrine-containing products (2001).

Table 5. Federal and State regulatory actions against Ephedra and ephedrine alkaloids (1989, Blumenthal 1997a, Blumenthal 1997b, Blumenthal 2000, Blumenthal & Dickinson 1996)

Date	Action	Authority
November 1989	Ephedrine and pseudoephedrine placed on a list of controlled substances used in the manufacture of illegal drugs	Drug Enforcement Agency (DEA)
1991–1994	State regulations controlling sale of ephedrine and/or Ephedra	Arizona, Arkansas, California, Florida, Hawaii, Idaho, Missouri, Nevada, New Mexico, Ohio, Oklahoma, Oregon, Texas, Virginia, Washington
1993	Exemptions for ma huang products with less than 25 mg of total ephedrine alkaloids	Arizona, Nevada and Washington
August 1994	Ephedrine placed into Schedule V of Ohio's Controlled Substance Act. Sale of Ephedra banned in Ohio	Ohio's Drug Laws Board
June 1996	Proposed warning and dose limitations on dietary supplements containing Ephedra	Food and Drug Administration (FDA)
January 1997	Texas withdraws proposed regulations to ban Ephedra	Texas Board of Health
March 1997	Ban on Ephedra sales amended in Ohio. Bill permits natural product stores to sell the herb containing limited alkaloid levels	Ohio's Drug Laws Board
February 2000	Withdrawal of proposed Ephedra rules	Food and Drug Administration (FDA)

In June 2002, the HHS Secretary announced new efforts to expand scientific research on the safety of ephedrine alkaloids and to aggressively pursue the illegal marketing of non-herbal synthetic ephedrine alkaloid products. Concerning scientific research, the HHS recently funded the RAND Corporation to conduct a comprehensive review of the existing science on ephedrine alkaloids, particularly those in dietary supplements. The National Institutes of Health (NIH) will use the resulting information to guide an expanded research effort to better understand the safety of ephedrine alkaloids. The FDA has also begun a major effort to strengthen its adverse event monitoring system by incorporating existing reporting systems into a new, unified reporting system to track and analyze adverse event reports. Concerning the legal issues, FDA has recently sent warning letters to firms unlawfully selling non-herbal ephedrine-containing products over the Internet. Six letters went to manufacturers of products that contain the drug ephedrine or norephedrine hydrochloride labeled as dietary supplements of use in weight loss, suppression of appetite, enhanced libido, and the like.

On the Canadian frontier, further steps have also been implemented. The Food Directorate included Ephedra in a list of herbs that are required to have a Drug Identification Number (DIN) from the Therapeutic Products Directorate before they can be sold in Canada. Health Canada has also published a guide for Ephedra labeling that limits indications to nasal decongestion and dosage to 8 mg of (–)-ephedrine every 6–8 hours (max 32 mg/day) (Cabrera, 1998). It is interesting to note that the Canadian approach actually materializes suggestions that were echoed in the US to handle the Ephedra situation. Such suggestions included limiting dosage to 10 mg total alkaloids per dose (40 mg/day), banning claims of energy or weight loss, specific labeling guidelines and the observance of good manufacturing practice (GMP) (Blumenthal and Dickinson, 1996).

CONCLUSION

As discussed earlier, the chemistry and pharmacology of Ephedra alkaloids as pure drug entities have been well established. Their adverse effects and toxicology have also been appropriately documented. Legislative and regulatory debates have been going on for many years. The pivotal question, then, becomes: is Ephedra safe? Is it effective? Should it be banned? Although a direct answer is not currently available, a number of pointers may help formulate a strategic solution and a future answer. Among such pointers are (i) the impact of overdosing on herbal supplements *vs* Over-the-Counter products; (ii) the general quality, safety and efficacy considerations pertaining to herbal products; (iii) risk/benefit balance in the use of herbal supplements in general and Ephedra in particular; (iv) public education toward the proper use of and expectations from herbal medicines. The first step toward a comprehensive answer is to properly approach the quality issue. Research funding and sponsorship should be the responsibility of the industry/trade councils, as well as specialized government institutes, such as the NIH's Office of Dietary Supplements (ODS) and National Center for Complementary and Alternatime Medicine (NCCAM). With a strong commitment from all involved parties, academic institutes will have the incentive to develop and expand their research/education programs toward establishing a scientific base capable of handling all relevant issues of herbal dietary supplements.

REFERENCES

Amatsu H, Kubota S. 1917. *Kyoto Igaku Zassi* **14**: 77.

Ang-Lee M, Moss J, Yuan C. 2001. Herbal medicines and perioperative care. *JAMA* **286**: 208–216.

Anonymous. 1989. Ephedrine supplies become tighter. *HerbalGram* **18/19**: 15.

Bensky D, Gamble A. 1993. *Chinese Herbal Medicine: Materia Medica*. Eastland Press: Seattle, WA.

Betz JM, Gay ML, Mossoba MM *et al.* 1997. Chiral gas chromatographic determination of ephedrine-type alkaloids in dietary supplements containing Ma Huang. *JAOAC Int* **80**: 303–315.

Bilia AR, Morelli I, Hamburger M, Hostettmann K. 1996. Flavans and A-type proanthocyanidins from *Prunus prostrata*. *Phytochemistry* **43**: 887–892.

Blumenthal M. 1997a. FDA proposes warnings and dose limits on Ephedra. *HerbalGram* **40**: 26–27.

Blumenthal M. 1997b. Ma huang update: Ohio Amends ephedrine ban/Texas pulls back proposed regulations banning Ephedra. *HerbalGram* **39**: 25.

Blumenthal M. 2000. Ephedra Update: Industry Coalition Asks FDA to Adopt National Labeling Guidelines on Ephedra; Offers Cooperative Research with NIH. *HerbalGram* **50**: 64–65.

Blumenthal M, Dickinson A. 1996. FDA hearing portends uncertain future for mahuang. *HerbalGram* **38**: 28–31.

Boozer CN, Nasser JA, Heymsfield SB, *et al.* 2001. An herbal supplement containing ma-huang-guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord* **25**: 316–324.

Cabrera C. 1998. Canadian regulatory update. *HerbalGram* **42**: 22.

Carey J. 2000. Herbal remedies: this market is a bit too free. *Business Week* **September 4**: 75–76.

Castledina RM, Harborne JB. 1976. *Phytochemistry* **15**: 803.

Chen AL, Stuart EH, Chen KK. 1931. The occurrence of methylbenzamine in the extract of ma huang. *J Am Pharm Assoc* **20**: 339–345.

Chen KK, Schmidt CF. 1926. The action and clinical use of ephedrine. *J Am Pharm Assoc* **87**: 836–842.

Chumbalov TK, Chekmeneva LN. 1976. *Khim Prir Soedin*: 543.

DePace A, Verebey K, ElSohly M. 1990. Capillary gas-liquid chromatography separation of phenethylamines in amphetamine-positive urine samples. *J Forensic Sci*: 1431–1435.

Dollery C. 1991. *Therapeutic drugs*. Churchill Livingstone Inc.: New York.

Engle AR, Lucas EA, Purdie N. 1994. Determination of enantiomers in ephedrine mixtures by polarimetry. *J Pharm Sci* **83**: 1310–1314.

Fetrow CW, Avila JR. 1999. *Complementary & Alternative Medicines*. Springhouse: Pennsylvania.

Friedrich VH, Wiedemeyer H. 1976. Quantitative bestimmung der gerbstoffblidner und der gerbstoffe in *Ephedra helvetica*. *Planta Med* **30**: 223–231.

Gay M, White K, Obermeyer W *et al.* 2001. Determination of ephedrine-type alkaloids in dietary supplements by LC/MS using a stable-isotope labeled internal standard. *J AOAC Int* **84**: 761–769.

Grue-Sorensen G, Spenser ID. 1993. Biosynthesis of the *Ephedra* alkaloids: evolution of the C_6–C_3 skeleton. *J Am Chem Soc* **115**: 2052–2054.
Gurley BJ, Gardner SF, Hubbard MA. 2000. Content versus label claims in Ephedra-containing dietary supplements. *Am J Health-Syst Pharm* **57**: 963–969.
Gurley BJ, Wang P, Gardner SF. 1998. Ephedrine-type alkaloid content of nutritional supplements containing *Ephedra sinica* (Ma-huang) as determined by high performance liquid chromatography. *J Pharm Sci* **87**: 1547–1553.
Haller C, Benowitz N. 2000. Adverse cardiovascular and central nervous system events associated with dietary supplements containing Ephedra alkaloids. *New Eng J Med* **343**: 1833–1838.
Hikino H. 1982. Structure of ephedrannin A, a hypotensive principle of Ephedra roots. *Tetrahedron Lett* **23**: 673–676.
Hikino H, Kiso Y, Ogata M, *et al.* 1984. Pharmacological actions of analogues of fruloylhistamine, an imidazole alkaloid of *Ephedra* roots. *Planta Med* **50**: 478–480.
Hikino H, Konno C, Takata H, Tamada M. 1980. Antiinflammatory principle of *Ephedra* herbs. *Chem Pharm Bull* **28**: 2900–2904.
Hikino H, Ogata M, Konno C. 1983a. Structure of feruloylhistamine, a hypotensive principle of Ephedra roots. *Planta Med* **48**: 108–110.
Hikino H, Ogata M, Konno C, Sato S. 1983b. Hypotensive actions of Ephedradines, macrocyclic spermine alkaloids of Ephedra roots. *Planta Med* **48**: 290–293.
Hoffman BB, Lefkowitz RJ. 1996. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, JG Hardman, LE Limbird, PB Molinoff, *et al.* (eds). McGraw-Hill: New York; 221–248.
Hosoya E. 1985. The pharmacology of kampo prescriptions. In *Herbal Medicine: Kampo, Past and Present*, T Takemi, M Hasegawa, A Kumagai, Y Otsuka (eds). Tsumura Juntendo: Tokyo; 52–65.
Hutchinson K, Andrews KM. 1995. *Microgram* **XXVIII**: 256–263.
Jones D. 1999. *Ephedra (Ma-huang); Today and Yesterday: Traditional and Topical Aspects of its Nutritional and Clinical Applications*. Presented at AHPA Ephedra International Symposium, Arlington, VA, December 1999.
Josefson D. 1995. Herbal stimulant causes US deaths. *Br Med J* **312**: 1378–1379.
Kasahara Y, Hikino H, Tsurufuji S *et al.* 1985. Antiinflammatory actions of ephedrines in acute inflammation. *Planta Med* **39**: 325–331.
Konno C, Mizuno T, Hikino H. 1985. Isolation and hypoglycemic activity of Ephedrans A, B, C, D and E, glycans of Ephedra distachya herbs. *Planta Med* **51**: 162–163.
Konno C, Taguchi T, Tamada M, Hikino H. 1979. Ephedroxane, anti-inflammatory principle of *Ephedra* herbs. *Phytochemistry* **18**: 697–698.
Lau O-W, Mok C-S. 1995. High-performance liquid chromatographic determination of active ingredients in cough-cold syrups with indirect conductometric detection. *J Chromatogr A* **693**: 45–54.
LeBelle MJ, Savard C, Dawson BA *et al.* 1995. Chiral identification and determination of ephedrine, pseudoephedrine, methamphetamine and metecathinone by gas chromatography and nuclear magnetic resonance. *Foren Sci Int* **71**: 215–223.
Leung AY. 1999. *Ephedrine, Ephedra, Mahuang, Mahuanggen-What are They*? Presented at AHPA Ephedra International Symposium, Arlington, VA.
Leung AY, Foster S. 1996. *Encyclopedia of Common Natural Ingredients*. John Wiley & Sons: New York.
Li H, Ding M, Yu J. 2001. Separation and determination of ephedrine alkaloids and tetramethylpyrazine in Ephedra sinica Stapf by gas chromatography-mass spectrometry. *J Chromatogr Sci* **39**: 370–374.
Ling M, Piddlesden SJ, Morgan BP. 1995. A component of the medicinal herb Ephedra blocks activation in the classical and alternative pathways of complement. *Clin Exp Immunol* **102**: 582–588.
Liu Y-M, Sheu S-J. 1993. Determination of ephedrine and pseudoephedrine in chinese herbal preparations by capillary electrophoresis. *J Chromatogr* **637**: 219–223.
Liu Y-M, Sheu S-J, Chiou S-H, *et al.* 1993. A comparative study on commercial samples of Ephedra herba. *Planta Med* **59**: 376–378.
Longo M, Martines C, Rolandi L, Cavallaro A. 1994. Simple and fast determination of some phenethylamines in illicit tablets by base-deactivated reversed phase HPLC. *J Liq Chromatog* **17**: 649–658.
Morton JF. 1977. *Major Medicinal Plants*. Charles C. Thomas: Illinois.
Murray M (ed.). 1995. Ephedra. In *The Healing Power of Herbs The Enlightened Person's Guide to the Wonders of Medicinal Plants, 2nd edition* (ed.). Prima Publishing.
Nadir A, Agrawal S, King PD, Marshall JB. 1996. Acute hepatitis associated with the use of a Chinese herbal product, mahuang. *Am J Gastroenterol* **91**: 1436–1438.
Nawwar MAM, Barakat HH, Buddrust J, Linscheid M. 1985. Alkaloidal, lignan and phenolic constituents of *Ephedra alata*. *Phytochemistry* **24**: 878–879.
Neuberg C, Hirsch J. 1921. *Biochem Z* **115**.
Reti L. 1953. Ephedra Bases. In *The Alkaloids*, RHF Manske, HL Holmes (eds). Academic Press: New York; 339–362.
Ros JJ, Pelders MG, De Smet PA. 1999. A case of positive doping associated with a botanical food supplement. *Pharm World Sci* **21**: 44–46.
Sagara K, Oshima T, Misaki T. 1983. A simultaneous determination of norephedrine, pseudoephedrine, ephedrine and methylephedrine in Ephedra Herba and oriental pharmaceutical preparations by ion-pair high-performance liquid chromatography. *Chem Pharm Bull* **31**: 2359–2365.
Samuelsson G. 1992. *Drugs of Natural Origin*. Swedish Pharmaceutical Press: Stockholm.
Shabana MM. 1990. Study into wild Egyptian plants of potential medicinal activity. Ninth communication: hypoglycaemic activity of some selected plants in normal fasting and alloxinated rats. *Arch Exp Veterinar Med* **44**: 389.
Skinner HF. 1990. Methamphetamine synthesis via hydriodic acid/red phosphorus reduction of ephedrine. *Forensic Sci Int* **48**: 123–134.
Song KS. 1994. *Arch Pharmacol Res* **17**: 54.
Starrat AN, Caveney S. 1995. Four cyclopropane amino acids from *Ephedra*. *Phytochemistry* **40**: 479–481.
Starrat AN, Caveney S. 1996. Quinoline-2-carboxylic acids from *Ephedra* species. *Phytochemistry* **42**: 1477–1478.
Takagi T, Itabashi Y. 1982. cis-5-Olefinic unusual fatty acids in seed lipids of gymnospermae and their distribution in triacylglycerols. *Lipids* **17**: 716–723.
Takahashi D, Miura K. 1888. *Mitt Med Fak Tokyo* **1**: 255.
Tamada M, Endo K, Hikino H. 1978. Maokonine, hypertensive principle of Ephedra roots. *Planta Med* **34**: 291–293.
Tamada M, Endo K, Hikino H, Kabuto C. 1979. Structure of Ephedradine A, a hypotensive principle of *Ephedra* roots. *Tetrahedron Lett* **10**: 873–876.
Taraskina KB, Chumbalov TK. 1970. *Khim Khim Tekhnol* **1**: 136.
Taraskina KB, Chumbalov TK, Ushakova MT, Arisinova AD. 1966. *Med Prom SSSR* **20**: 27.
Tyler VE. 1999. *Tyler's Honest Herbal*. Haworth Herbal Press: New York.
Vallerand A. 1993. Effects of ephedrine/xanthines on thermogenesis and cold tolerance. *Int J Obesity* **17**: S53–S56.
van der Merwe PJ, Hendrikz SE. 1995. Identification of ephedrines as their carbon disulfide derivatives. *J Chromatogr B* **663**: 160–166.
Vansal S, Feller D. 1999. Direct effects of ephedrine isomers on human β-adrenergic receptor subtypes. *Biochem Pharmacol* **58**: 807–810.
Weiss RF. 1988. *Herbal Medicine*. AB Arcanum: Avon.
Welsh LH. 1947. Report on the determination of ephedrine. *JAOAC Int* **30**: 467–473.
Zaacks SM, Klein L, Tan CD, Rodriguez ER, Leikin JB. 1999. Hypersensitivity myocarditis associated with Ephedra use. *Clin Toxicol* **37**: 485–489.

