Pharmacological Effects of Ephedrine

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Abstract

Ephedrine is a sympathomimetic agent that has widespread use as an adrenergic stimulant. It comes from plants of the genus *Ephedra* sp., being an alkaloid mainly found in the specie *Ephedra sinica*. This amine can be obtained by industrial synthesis, as a product of biotransformation or by extraction of the plant. Other derivatives of ephedrine can also be found in *Ephedra*, such as

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pseudoephedrine that also has adrenergic activity. The purest form of ephedrine is used for therapeutic purpose, primarily as a bronchodilator and decongestant. Its pharmacological applications are related to its sympathomimetic properties, which in turn occur due to its stimulating action on α-, β1-, and β2-adrenergic receptors through direct and indirect effects. Nowadays, there is a concern about the indiscriminate use of ephedrine, since it started to be used to weight loss and enhance athletic performance. Associated with this tendency, a large number of adverse effects related with cardiovascular issues started to be reported. This chapter will discuss botanical, chemical, pharmacological, toxicological, and analytical aspects of ephedrine.

Keywords

Ephedra • Ephedraceae • Ephedrine • Phenylethylamine alkaloid • Sympathomimetic amine

Abbreviations

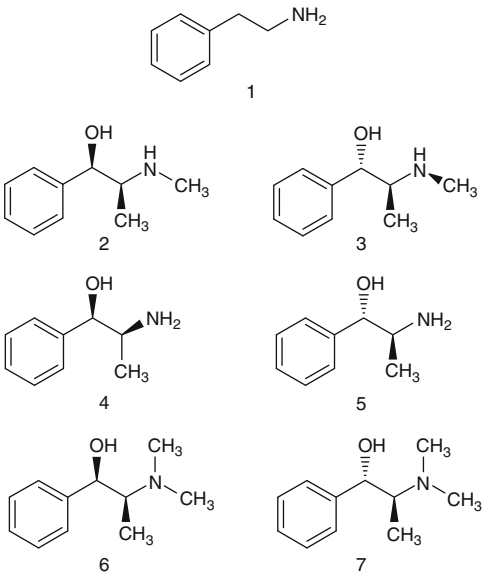
AMP	Adenosine 3′,5′-monophosphate
CE	Capillary electrophoresis
CNS	Central nervous system
GC–FID	Gas chromatographic–flame ionization detector
GC–MS	Gas chromatographic–mass spectrometer
GC–NPD	Gas chromatographic–nitrogen–phosphorus detector
GCxGC	Gas chromatographic–gas chromatographic
HS	Headspace
LC–MS/MS	Liquid chromatographic–mass spectrometer mass spectrometer
LC–UV	Liquid chromatographic–ultraviolet
LLE	Liquid–liquid extraction
MAO	Monoamine oxidase
NE	Norepinephrine
PAL	L-phenylalanine ammonia-lyase
Phe	L-phenylalanine
SPE	Solid-phase extraction
SPME	Solid-phase microextraction
TLC	Thin-layer chromatography
VMT	Vesicular monoamine transporter

1 Introduction

Ephedrine (1*R*-2*S*-2-methylamino-1-phenylpropan-1-ol) is an adrenergic amine present in many kinds of pharmaceutical preparations, obtained by synthesis or from natural sources. Belonging to the genus *Ephedra* (Ephedraceae), the Chinese species *Ephedra sinica* and *Ephedra equisetina*, also known as ma huang, and the Indian and Pakistani species *E. gerardiana*, *E. intermedia*, and *E. major* are the

primary source of ephedrine [1]. Besides *Ephedra* species, low amounts of ephedrine (less than 2 %) can also be found in the leaves of the Malvaceae *Sida cordifolia* (Linn) (known as country mallow) [2, 3] and in the Chinese herb *Pinellia* (known as ban xia), with around 0.003 % of ephedrine [4].

Ephedrine belongs to β-phenylethylamine core structure (**1**) and is kinetically and dynamically close related to amphetamine-type derivatives that include stimulants, psychedelics, and entactogens, as well as anorectics, bronchodilators, decongestants, and antidepressants [5]. Ephedrine (**2**) and its analogues pseudoephedrine, norephedrine (phenylpropanolamine) and norpseudoephedrine (cathine), as well as methylephedrine and methylpseudoephedrine (**3–7**) cannot be considered typical alkaloids, since they do not have the nitrogen as part of a heterocyclic ring system, being called protoalkaloids into the *sensu lato* alkaloid class [1].



The medicinal herb *Ephedrae* (ma huang or merely "ephedra") has been millenary used in traditional Chinese medicine to induce perspiration, reduce fever, and treat coughs and asthma. Recently, *Ephedra*-containing dietary supplements have been used as an aid in diets and as a stimulant to boost energy and athletic performance. The activity of ephedra is attributed to the presence of three pairs of diastereoisomeric alkaloids: (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine, (1*R*,2*S*)-(−)-norephedrine and (1*S*,2*S*)-(+)-norpseudoephedrine, and (1*R*,2*S*)-(−)-*N*-methylephedrine and (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine (**2–7**), being ephedrine the major constituent of it. More than 50 species of *Ephedra* are known and at least 18 of them contain these alkaloids. The amounts of ephedrines vary according to the species, time of harvest, geographical location, and growing conditions [6].

The long history of *Ephedra*'s use has begun in oriental medicine, especially for the treatment of asthma, colds, cough, fever, headache, and nasal congestion [7, 8]. Some applications still remain in modern medicine, but much has changed after the beginning of ephedrine's use for weight loss and muscle gain [9]. The record of cardiovascular adverse effects attributed to the use of ephedrine usually associated with others substances such as caffeine, salicin, and/or p-synephrine led to a higher concern about the use of this amine. Thus, after several attempts, the FDA banned the sale of ephedrine-containing products in the United States [10]. However, the pharmacological and toxicological properties strongly depend on the concentration of ephedrine, interactions with other drugs, individual susceptibility, and the presence of contaminants [8].

Based on these considerations, this chapter presents a literature review over several aspects of ephedrine, focusing on its botany, chemical composition, general uses, pharmacological properties, toxicity, and analytical aspects.

1.1 Occurrence

Plants of the genus *Ephedra* sp. (Ephedraceae, Gnetales) are the main natural source of ephedrine and related alkaloids. The aerial parts of different *Ephedra* species contain at least six optically active constituents that are structurally related to ephedrine. Among these, ephedrine and pseudoephedrine are the main psychoactive constituents, although others as optical isomers and methylated derivatives are also important [11].

A major source of *Ephedra* is near to the seacoast in southern China and this local formerly supplies most of the American market [12]. These popular herbs, also known as ma huang in traditional Chinese medicine, can be found in subtropical zones in Asia, Europe, and America [8, 13]. The name ma huang has Chinese origins, in which "ma" means astringent and "huang" means yellow, probably referring to the taste and color of the plant or tops of *Ephedra sinica* Stapf [12].

The *Ephedraceae* family consists of branched shrubs, rarely being small trees, with opposite leaves, scales and very small size [14]. The shrubs can reach 1 m in height and can grow in semiarid and desert conditions, being the six continents suitable for the growth of that genus [15]. Studies indicate that there are between 50 and 65 species of *Ephedra* in the world [16]. The plants are small bushes, dioecious, and with minute leaves, giving the appearance of leafless shrub. The shrub grows 60–90 cm high and has slender aerial stems, which are green, erect, small ribbed, and channeled. It is 1.5 mm in diameter and usually terminates in a sharp point. At the nodes, which are 4–6 cm apart, the leaves appear as whitish, triangular, scarious sheaths. Small blossoms appear in the summer [12, 17]. The concentration of ephedrine alkaloids can vary from 0.02 % to 3.40 % according to species and the isomer (−)-ephedrine represents from 30 % to 90 % of the total content of alkaloids [17, 18].

The different proportions of the alkaloids vary between plants of the same species and between different species of the genus *Ephedra* [19]. The collection

aspects are also important. The plant should be collected in the autumn, since the amount of alkaloid shows considerable variation at different seasons [1].

Ephedrine and pseudoephedrine are the main active constituents of the *Ephedra*. Described in pharmacopoeias of China, Germany, and Japan, the dried young branches of *Ephedra sinica, E. equisetina*, *and E. gerardiana* contain not less than 1.25 % of alkaloids [20]. Japanese pharmacopoeia specifies not less than 0.6 % [21].

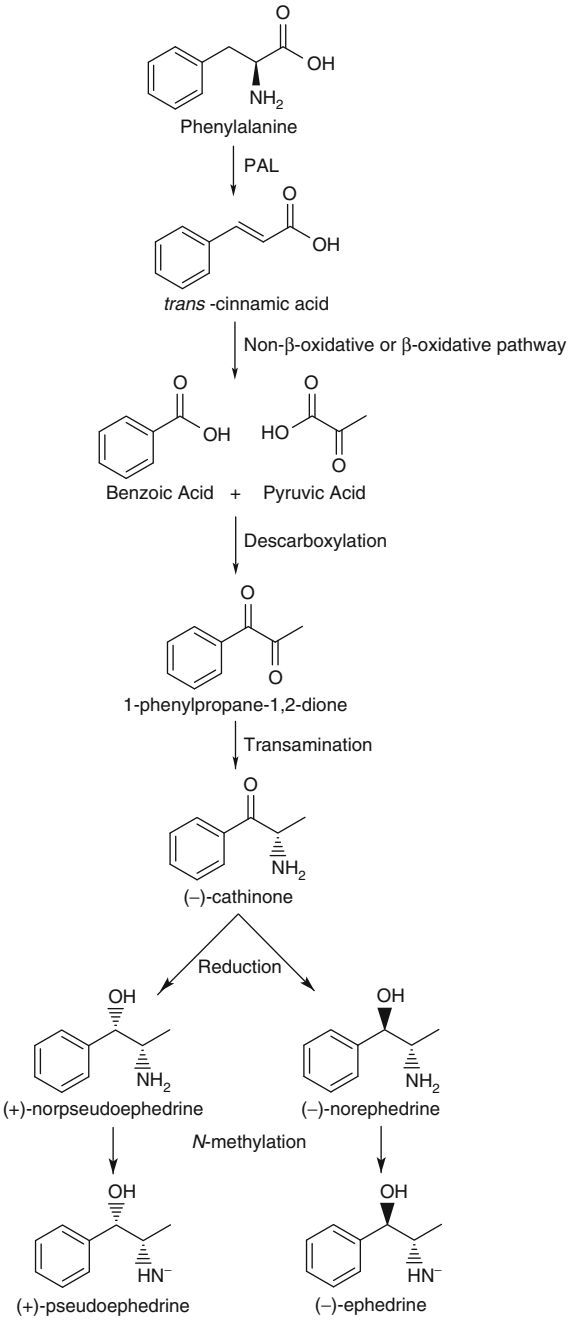
Ephedra sinica is the primary source of ephedrine alkaloids, although other species of this genus may contain the active constituents as *E. equisetina, E. intermedia*, *E. gerardiana, E. alata*, *E. distachya, E. botschantzevii*, *E. fragilis, E. major*, *E. minuta, E. monosperma*, *E. pachyclada, E. likiangensis*, *E. saxatilis, E. lomatolepis*, *E. lepidosperma, E. przewalskii*, and *E. regeliana* [22]. Eurasian species are characterized by the presence of alkaloids, while American species are considered devoid of such metabolites [7, 22–24]. Approximately 40 species of *Ephedra* are grown for commercial purposes; among them are *Ephedra sinica* Stapf and *E. equisetina* Bunge, from southern China, and *E. intermedia* Schrenk and *E. gerardiana* Wall, from India and Pakistan [17, 25]. The less-known alkaloid ephedroxane was found in *Ephedra intermedia* and at least in six more species [26].

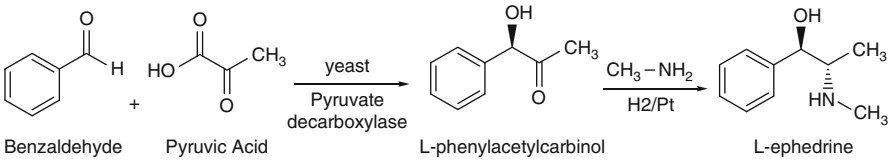
Besides *Ephedra* species, low amounts of ephedrine can also be found in the leaves of the Malvaceae *Sida cordifolia* (Linn) (known as country mallow), with less than 2 % of content [2, 3] and in the Chinese herb *Pinellia* (known as ban xia), with around 0.003 % of ephedrine [4, 27]. Due to the low content of ephedrine, no stimulatory effects were observed in pharmacological tests with *Pinellia*, showing the opposite effect of sedation [28]. In addition to other species previously mentioned, other monoamine alkaloids can be found in khat (*Catha edulis* Forsk.) such as norpseudoephedrine and norephedrine [29, 30].

1.2 Biosynthesis and Chemical Aspects

L-phenylalanine (Phe) is the precursor of the biosynthesis of ephedrine in plants, unlike the majority of alkaloids [31]. Although the backbone of this amino acid has clear resemblance with ephedrine, phenylalanine provides only the aromatic ring and the first carbon of the side chain (C1–C6) of this amine. Supporting this finding, it was shown that cinnamic acid, benzoic acid, and benzaldehyde are easily incorporated into ephedrine [32], being the remaining two carbons (C2–C3) derived from pyruvate and the nitrogen introduced by reaction of transamination at the end of biosynthesis, as can be seen in Scheme 38.1 [33, 34]. The biosynthetic route from phenylalanine occurs with the metabolism of L-phenylalanine through cinnamic acid to benzoic acid. The conversion of phenylalanine into *trans*-cinnamic acid is well characterized by the enzyme L-phenylalanine ammonia-lyase (PAL) [35]. At least two possible courses of Phe side-chain shortening is currently accepted in benzoic acid biosynthesis: the β-oxidative and non-β-oxidative pathway [36]. Besides PAL, no other enzymes involved in biosynthesis of amphetamine analogues were isolated [31]. Benzoic acid may undergo esterification with coenzyme

Scheme 38.1 Biosynthesis of ephedrine and related alkaloids





Scheme 38.2 Synthesis of ephedrine by fermentation reaction on benzaldehyde, followed by reductive condensation with methylamine

A following by acetylation with pyruvate, which in turn is decarboxylated to diketone. A transamination reaction occurs with diketone giving cathinone. Reduction of the carbonyl group of cathinone provides norephedrine or norpseudoephedrine which in turn suffer *N*-methylation generating ephedrine or norpseudoephedrine [37].

The ephedrine and pseudoephedrine commercially available and used for medicinal purposes are obtained either synthetically or by the extraction of plant material. Three possible methodologies can be used for the commercial production of ephedrine. The first one is the extraction from plants, especially from those of the genus *Ephedra*, and it is still used for herbal formulations, although being an expensive and prolonged method. The extraction method consists basically in the treatment of the alkaloids with alkali followed by addition of an organic solvent to extract the substance [31]. The commercial production can also occur by a chemical synthesis that has been developed to obtain racemic mixtures of ephedrine [38]. The third method is the most common and consists of a combination of fermentation and chemical synthesis, being a semisynthetic process. [31]. It involves the biotransformation of benzaldehyde to L-phenylacetylcarbinol, catalyzed by the enzyme pyruvate decarboxylase. The chemical procedure of fermentation usually uses brewer's yeast (*Saccharomyces* sp.) or others species of yeast. The chemical counterpart of the method is based on a reductive condensation with methylamine in combination with hydrogen and metals as catalysts, as shown in Scheme 38.2. The growth phase is followed by biotransformation and added sugars, seeking to maximize L-phenylacetylcarbinol production. This process yields (−)-ephedrine with very high enantioselectivity, [12, 17], being (1S,2R)-pseudoephedrine produced from its diastereomer via Welsh rearrangement [31].

Considering the chemical characteristics, ephedrine has two chiral centers, and therefore four isomers can be identified: (±)-ephedrine and (±)-pseudoephedrine [39]. (1R,2S)-(−)-ephedrine is the major isomer found in Ephedra sp., and pharmacological studies have shown it as responsible for the pharmacological activities of ephedra. Not only (−)-ephedrine has the widespread use but also (+)-pseudoephedrine is added in over-the-counter decongestant preparations [40]. The four isomers of ephedrine may be naturally present in *Ephedra* species, and they are usually used as a hydrochloride form, being the classical purification method for ephedrine hydrochloride a combination of conventional infusion and organic solvent extraction or adsorption [41]. Other alkaloids are also present in smaller amounts, and the minor ephedrine alkaloids include (+)-pseudoephedrine and the demethyl analogues (−)-norephedrine and (+)-norpseudoephedrine [40].

Ephedrine occurs as white, rosette, needle, and crystals. It is soluble in water, alcohol, chloroform, ether, and in liquid petrolatum [12] and has a melting point of 187 °C–188 °C. It is marketed as ephedrine hydrochloride and may be found some traces of benzoic acid as a by-product of the process [42].

1.3 Analytical Aspects

A great number of publications on ephedrine-containing products analysis are proposed in the literature [43]. Extraction of ephedrines in body fluids and pharmaceuticals using liquid–liquid extraction procedures (LLE), solid-phase extraction (SPE), solid-phase microextraction (SPME), and headspace (HS) have been reported [44]. Gas chromatographic (GC) and liquid chromatographic (LC) procedures with different detectors (e.g., mass spectrometer, MS; nitrogen–phosphorus detector, NPD; flame ionization detector, FID; and ultraviolet, UV) have been used as analytical strategies, in addition to immunoassays, thin-layer chromatography (TLC), and capillary electrophoresis (CE). The employ of them depends on the purpose of analysis and the kind and amount of matrix used. Ephedrine-related compounds may be quantified in blood, plasma, or urine to monitor possible abusers, such as athletes, or to confirm a diagnosis of poisoning and to assist a medicolegal death investigation.

The choice of the method depends on the sensitivity and the resolution required for the analysis, the complexity of the sample matrix, and the time needed for sample pretreatment. Considering that extracts of the plants are a complex matrix, the analysis need to be preceded by preparative methodologies in order to clean up the samples. Nowadays, solid-phase extraction (SPE) is considered the gold standard for pretreatment of samples. This methodology allows the passage of large volumes of sample through the extractor column, which will selectively retain the analytes. The interfering compounds can then be discarded and the previously retained analytes are eluted with small amounts of organic solvent in a concentration range suitable for instrumental analysis. SPE also pre-concentrate the analyte, improving the sensitivity of the analysis [24] consisting in a better approach when compared with liquid–liquid extraction.

Analytical strategies including GC–NPD [45], GC–FID [46], GCxGC [47], GC–MS [48–50], LC–UV [6, 51], and LC–MS/MS [6, 52–55] have been employed in the routine laboratories to normal and chiral analysis. The use of mass spectrometry detection is mandatory to the confirmatory steps of the analyses. Methods by CE have been successfully used to separate chiral isomers of ephedrine and related compounds [56, 57]. Chromatographic techniques can easily distinguish (−)-ephedrine from other phenylethylamine derivatives and diastereoisomers.

LC–MS/MS procedures have the advantage of decrease work-up time due to the ability to analyze underivatized compounds. These techniques have also shown the ability to separate structural isomers such as norpseudoephedrine and norephedrine with relatively short analysis times, having a reported instrument cycle time of 8 min per sample [53, 58]. Currently, GC–MS is still the preferred method for

forensic confirmation and has the advantage of low equipment costs. However, a previous derivatization step should be employed in order to improve the accuracy and the chromatographic profile of the analysis. An attractive analytical approach for routine confirmations can be created by combination of extractive–derivatization techniques with fast GC–MS, considering that the analytes of interest are separated by chromatography and accurately quantified [59], through a well-validated method.

2 Pharmacological Applications

Ma huang is one of the oldest known drugs and has been used as a medicine in China for more than 5,000 years [17]. Its use in modern medicine began in 1923 with the discovery of the valuable properties of ephedrine [12] which in turn was discovered in 1887 [37].

Ephedrine is a sympathomimetic amine with similar effects to those of adrenaline, so it is taken most commonly as a decongestant or for weight loss and energy enhancement as a dietary supplement [17, 60]. The purest form of ephedrine is currently used as a bronchodilator, decongestant, and vasopressor due to its sympathomimetic effects. The bronchodilator activity promotes relief in asthma, relaxing the bronchial smooth muscle in asthmatic patients. The vasoconstrictor action on mucous membranes makes it a superior nasal decongestant [17], being that the main clinical use for ephedrine. It may be used alone or in combination with other agents for the relief of cold symptoms being used topically and orally [20].

Other presentations of ephedrine have the same or very similar clinical uses. Ephedrine sulfate, for example, is used to combat hypotensive states, nasal congestion, and allergic disorders, such as bronchial asthma. Ephedrine hydrochloride is used similarly to ephedrine as a sympathomimetic agent [12]. Ephedrine hydrochloride or sulfate has been used as a bronchodilator, but the more selective β2-sympathomimetic bronchodilating agents, such as salbutamol, are now preferred. The salts of ephedrine have been given parentally to combat a fall in blood pressure during spinal anesthesia, since ephedrine is no longer generally advocated for orthostatic hypotension due to risk of shock, circulatory collapse, or hemorrhage. They are sometimes used in motion sickness, usually associated with hyoscine or an antihistaminic. Other uses include diabetic neuropathic edema and nocturnal enuresis, although other treatments are usually preferred [20]. Ephedrine derivatives are also largely employed, being pseudoephedrine widely used for the treatment of cough and cold and as a decongestant [17].

Besides the features already mentioned, ephedrine has also the capacity to stimulate thermogenesis in human subjects [61]. Probably because of its ability to stimulate the CNS and thermogenic properties, ephedrine may be employed to lose weight and enhance performance in endurance training and body building [62]. Thus, this pharmacological property triggered an unbridled use of it as a weight-loss compound, as well as an enhancer of athletic performance. So, ephedrine became quickly one of the main active components used in dietary supplements,

gaining market share. The marketing of ephedrine for this purpose was restrained only after serious adverse effects reports arising from its use. Thus, the toxicity of this alkaloid began to be studied in order to determine the toxicological profile of this amine either alone or in combinations with stimulants such as caffeine. Ephedrine is considered nowadays one of the substances most widely used in sport, together with amphetamines, cocaine, caffeine, and anabolic steroids [63].

Owing to its sympathomimetic activity, ephedrine may be contraindicated for individuals with hypertension or other cardiovascular diseases, glaucoma, diabetes, and hyperthyroidism [64].

It is currently being traded as "herbal ecstasy" due to its CNS stimulation that in overdoses can lead to hallucinations, paranoids, and psychosis [17]. However, the large number of reports of serious adverse effects related to the use of this substance increased the attention to its use.

3 Mechanism of Action

The adrenergic effects caused by ephedrine occur mainly due to its capacity to be a sympathomimetic agonist at both α- and β-adrenergic receptors. As consequence of these stimulations, an increase in cardiac rate and contractility, peripheral vasoconstriction, bronchodilation, and CNS stimulation can be observed as general effects caused by the use of this amine [62, 65].

Ephedrine stimulates α-, β1-, and β2-adrenergic receptors through direct and indirect effects on adrenergic receptors [20]. The β-adrenergic effects are believed to be pronounced by the activation of adenylcyclase which increases the productions of cyclic AMP, while α-adrenergic effects result from inhibition of adenylcyclase [12].

Considering the chemical structure of ephedrine, it is interesting to observe the lack of the phenolic group, characteristic of catecholamines. However, ephedrine remains capable to stimulate α- and β-receptor directly and displace norepinephrine (NE) from storage vesicles, releasing these catecholamines at synaptic areas in the brain and in the heart. These released substances act on receptors promoting the adrenergic effect [17, 66].

Due to this mechanism of releasing catecholamines, ephedrine is also classified as indirect-acting sympathomimetic amine. The chemical similarity between ephedrine and epinephrine allows the transport of ephedrine into the nerve terminal by NE transporter. Inside the terminal nerve, an exchange of NE by ephedrine occurs by the vesicular monoamine transporter (VMT). Thus, NE accumulates in cytosol, being part of it degraded by MAO and partly released in the synaptic cleft by NE transporter. This causes an increase in the amount of NE in the synaptic cleft and consequently increases the effect on noradrenergic postsynaptic receptors. Although the indirect action of ephedrine is well established, it is known that there are other adrenergic mechanisms, such as direct stimulation of adrenergic receptors, inhibition of NE transporter (NE remains longer in the synaptic cleft), and partial inhibition of MAO (the metabolism of NE is reduced) [63].

As expected, there are many drugs that can strongly interact with ephedrine, increasing or decreasing its effect. Classically, these drugs are those capable of modifying the noradrenergic transmission. So, MAO inhibitors potentiate the effect by preventing the inactivation of NE previously displaced from the vesicle. Drugs that inhibit NE transport prevent the catch of ephedrine by the nerve endings, decreasing the ephedrine effect [63].

By the mechanisms mentioned above, it is possible to correlate the clinical effects observed with the use of ephedrine, as well as to establish the possible effects before the consumption. The use of ephedrine in therapeutic doses raises the blood pressure by increasing cardiac output and also by inducing peripheral vasoconstriction. It may cause tachycardia. Its action on β- adrenergic receptors in the heart produces a positive ionotropic effect. Ephedrine has a stimulant action on the respiratory center. It also causes bronchodilatation, reduces intestinal tone and motility, and usually reduces the activity of the uterus. Its effects on α-adrenergic receptors results in vasoconstriction in the skin and mucous membranes [12], leading to hypertension, which may produce cerebral hemorrhage and pulmonary edema.

Sympathomimetic agents are capable to produce a wide range of adverse effects, most of which are due to excessive stimulation of the sympathetic nervous system. Therefore, these effects depend on the relative agonist activity of the drug at a given dose on different types of receptor. General adverse effects related to the use of sympathomimetic agents are fear, anxiety, restlessness, tremor, insomnia, confusion, irritability, and psychotic effects. Cardiovascular issues such as tachycardia and cardiac arrhythmias, angina pain, palpitations, and cardiac arrest may be produced by stimulation of β1-adrenergic receptors of the heart. On the other hand, vasodilatation caused by β2-stimulation may lead to hypotension with dizziness and fainting and flushing. These kinds of stimulants have important effects on the CNS. The development of tolerance and dependence and the significant abuse of these drugs are consequences related to the CNS effects of ephedrine [20].

Considering the foregoing, it is reasonable to recommend patients at risk of stroke, myocardial infarction, uncontrolled blood pressure, seizures, and general anxiety disorder to avoid ephedrine [67].

4 Toxicity

If used for therapeutic purposes with dose control, ephedrine has no potential toxicity. However, the toxicity of this amine may be expressed in overdosages, which can lead to paranoid psychosis, delusions, and hallucinations [20]. Large doses of ephedrine may cause hypertension, headache, dizziness, palpitations, vomiting, nervousness, and insomnia [12].

Nowadays, the use of ephedrine with nontherapeutic purpose, being marketed as an herbal or a dietary supplement containing *Ephedra* species, is common. The whole issue with *ephedra* alkaloids is most of the time a paradox: depending on the relevant legislation of each country, the whole extract is considered a supplement,

while the purified or synthesized alkaloids are considered pharmaceuticals being marketed as drugs. This usually means that the manufacturers of the alkaloid are compelled to prove both safety and efficacy of their products through clinical trials before being allowed to bring them to market, while the supplements have less demanding legislation [68]. Since ephedrine has thermogenic properties and is capable to stimulate lipolysis, the use of this amine had turned the attention to promote weight loss and improve athletic performance. Then a variety of compounds containing ephedrine, mainly dietary supplements, appeared on the market, being marketed with the appeal of easily promoting weight loss. Besides, the increasingly widespread use has been accompanied by the misconception of safety of ephedrine, mainly due to its natural origin [60]. In these cases, the use of ephedrine does not obey doses and leads to an uncontrolled consumption pattern often related to overdoses. Furthermore, there is no reliable quality control of these products due to a lack of effective monitoring on it, becoming difficult to ensure that the levels of ephedrine are consistent with that expressed in the label.

Scientific papers report that the pharmacological and toxicological properties of *Ephedra*-containing products depend strongly on the content of ephedrine and other associated substances. Clinical and preclinical studies and the long history of use of *ephedra* and its alkaloids indicate that its use can be safe if administrated according to the recommendations of the official codes. The serious adverse effects observed are related mainly to its overuse in dietary supplement formulations, to the associations and interactions with other drugs, individual susceptibility, and presence of contaminants, among other factors. Thus, the knowledge of the chemical composition of species of *Ephedra* and the correct orientation are essential to prevent accidents [8].

The study of the toxicity of commonly used associations became important when considering that it may cause an increase in cardiovascular risks when ephedrine is associated with other substances. Among the possible associations, the combination of ephedrine with *p*-synephrine (*Citrus aurantium* extract), salicin, and caffeine is one of the most usually found in the market, and it is used as an athletic performance enhancer and as a weight-loss compound. Recent studies have elucidated the acute and subchronic toxicity of this association. In the acute toxicity test in mice for both sexes, there were observed signs of toxicity such as ptosis, piloerection, and alterations in locomotor activity in all doses. A curious difference between genders not previously related in the literature was found. Signs were more intense in males possibly due to hormonal or metabolic differences. Other findings were alterations in locomotor activity, motor coordination, and body temperature, besides death by cardiopulmonary hemorrhage, corroborating with clinical reports that indicated the association of *p*-synephrine, ephedrine, and caffeine as potentially toxic [69]. These data indicate that the mechanism of action and toxicity of the mixtures is more complex than it was taught, involving alterations in the pharmacokinetic and pharmacodynamic properties when the substances are administered together, promoting unexpected adverse responses [69]. The results of subchronic test in rats helped to establish the toxicological profile of the association. The repeated dose given orally showed no clinical signs of toxicity, neither weight

alterations nor deaths occurred as well as any significantly alterations in hematological parameters. There were observed lipid peroxidation, hepatic and renal damages, and a reduction in glutathione levels in male rats. In females, there were no alterations observed, showing again the different toxicity profile displayed by male and female probably due to hormonal influence. Although results showed the capacity of the association to change the oxidative status and promote renal and hepatic damages, it is still necessary that more studies be conducted to elucidate the role of hormones on toxicological effects presented by the weight-loss association [70].

The toxicity of ephedrine is closely related to adverse cardiovascular events, since the clinical presentation of toxicity reflects the sympathomimetic activity of these agents. The adrenergic effects can shorten cardiac refractory periods, permitting the development of reentrant cardiac arrhythmias. The worst complication related to the use of ephedrine is thrombotic stroke, presumably resulting from vasoconstriction of large cerebral arteries that in turn leads to local thrombosis [71]. Other adverse effects include hypertension, diaphoresis, hypothermia, and agitation. The best treatment in an overdose is the rapid identification of the symptoms followed by supportive management.

Arbo and coworkers [72] performed a study to evaluate the female reproductive toxicity of *E. sinica*, *C. aurantium*, ephedrine, and *p*-synephrine. The uterotrophic assay was used, which is commonly applied to detect (anti)estrogenic activity of chemical substances or mixtures. Ephedrine at the dose of 0.5 mg/kg/day showed a reduction of the uterus relative mass, indicating an antiestrogenic effect of this amine. However, the authors emphasized the need of more studies to completely characterize the mechanism of action of ephedrine in the endocrine system, since the uterotrophic assay is only a screening assay. Another interesting result obtained in this study was a reduction in the adrenals relative mass in the groups which received ephedrine, *p*-synephrine, and both doses of the extracts. The authors attribute this finding to the α1-adrenoceptor agonist activity of these substances through the vasoconstriction and reduction of the liquid in the organ [72].

In 2004, the Food and Drug Administration banned the sale of ephedra-containing over-the-counter dietary supplements due to a several number of reports involving adverse effects related to its use [73]. However, these products remain available to the public through illicit channels. Anticipating the possible ban of ephedrine sales, the industry of supplements quickly reformulated and developed "Ephedra-free" products, intending to replace those which contain ephedrine. The strategy used was the replacement of ephedrine by *p*-synephrine, a structural analogue of ephedrine primarily found in *Citrus* sp. extracts. There are two chemical differences between ephedrine and *p*-synephrine: the presence of a hydroxyl group replacing a hydrogen atom and the absent of a side-chain methyl group replaced by hydrogen, both in *p*-synephrine. It is believed that the pharmacological effects of *p*-synephrine do not differ from ephedrine, providing the same stimulatory and potentially toxic effects on the CNS and cardiovascular system as ephedra [74]. The lipolytic effect of *p*-synephrine is alleged to occur by specific stimulating of β3-adrenergic receptor, and consequent thermogenesis [75, 76] is questionable.

In spite of its popularity, there is no strong evidence confirming the effectiveness of *p*-synephrine as a thermogenic agent. The use of *p*-synephrine in dietary supplements has been accompanied by human toxicity reports, which lead to the idea of high toxicity of this amine. The most common adverse effects were the cardiovascular ones, as well as those that happened with ephedrine. However, the complex combination of different compounds must be considered, since *Citrus* extracts contain other compounds than *p*-synephrine. The presence of contaminants or other stimulants may influence the pharmacological and toxicological profiles of the products, being difficult to attribute the occurrence of adverse events only to *p*-synephrine [77].

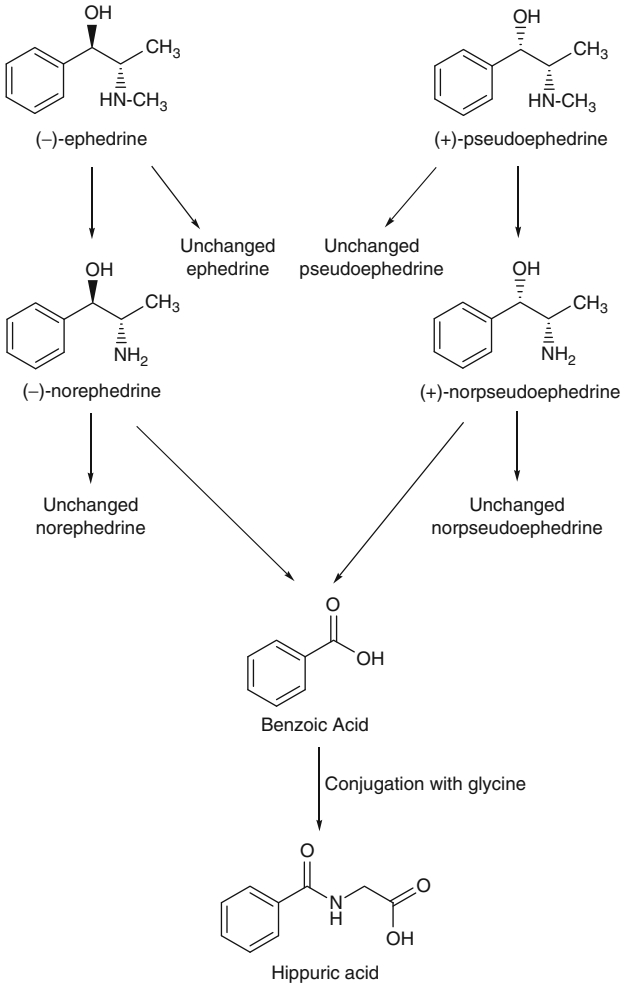
Considering that, studies have been developed to establish the toxicological profile of *p*-synephrine. The acute administration of *C. aurantium* extract (2.5 % *p*-synephrine) and *p*-synephrine produced reduction in locomotor activity, gasping, exophthalmia, piloerection, and salivation, corroborating to the hypothesis that *p*-synephrine acts not only in β3-adrenoreceptors but also in other adrenergic receptors. However, all the effects were reversible and persisted for 3–4 h. The adrenergic stimulation alerts for the same possible side effects of *p*-synephrine and *C. aurantiu*m [78]. The subchronic toxicity of *Citrus aurantium* extract and *p*-synephrine were also determined and indicated a low subchronic toxicity in mice but a possible alteration in the oxidative metabolism [79].

5 Bioavailability and Metabolism

The administration of ephedrine may be given orally or topically as nasal drops or sprays [20].

Ephedrine is orally active, being readily and completely (about 100 %) well absorbed from the gastrointestinal tract after oral administration. It has longer duration though less potent action than epinephrine [17, 20, 80]. The absorption is better with the oral administration of the pure alkaloid than with herbal alkaloid extracts, which the presence of many others substances may retard the rate of absorption. The heat stress may increase the absorption rate of ephedrine [81], as well as it may elevate blood pressure significantly greater under these stress conditions. Considering that *Ephedra* extracts are often taken prior to exercise in a warm environment, these stress conditions may enhance the cardiovascular effects experienced during physical activity [68].

Ephedrine has a large volume of distribution and is not bound to plasma proteins, remaining in the free form with high tissue affinity and capacity to reach high concentrations in the CNS. High doses of sympathomimetic drugs may cross the blood–brain barrier due to lipophilic properties of the molecule and therefore exercise adrenergic stimulation on the CNS, especially when orally administrated [82]. This amine is reported to have a plasma half-life ranging from 3 to 6 h, but its effects last about 1 h. The plasma half-life is influenced by the elimination process, which in turn depends on the urinary pH, since in acid urine, the elimination is enhanced, being the half-life in these cases accordingly shorter [20, 80].



Scheme 38.3 Biotransformation and excretion of ephedrine

Ephedrine undergoes hepatic biotransformation being excreted mostly unchanged in urine [83]. From 8 % to 20 % of ephedrine is excreted after demethylation and delamination according to its metabolism showed in Scheme 38.3.

Excretion is dependent on several factors including urine volume, urinary pH, and individual variability. Ephedrine and amphetamines are weak organic bases, and therefore, they are easily ionized in acidic medium because of an ionizable amino group on the molecule. The acidification prevents reabsorption promoting excretion because of the positively charged amino group. Alkaline urine has the opposite effect [84, 85]. The excretion of ephedrine also occurs in breast milk and crosses the placenta, which poses concerns for women who may be taking ephedrine during pregnancy or breast-feeding. It is excreted primarily

unchanged and with small amounts of metabolites in the urine over 24 h [20]. It is resistant to metabolism by monoamine oxidase, increasing its activity by oral ingestion.

6 Clinical Trials

Ephedrine is the most commonly used drug among the vasopressors to prevent hypotension during spinal anesthesia. A study randomized 42 women undergoing elective Cesarean section under spinal anesthesia into two groups (n = 21 per group), a control and an ephedrine-treated group. Shortly after the spinal injection, ephedrine 0.5 mg/kg in the ephedrine group or saline in the control group was injected intravenous for 60 seconds. The mean of highest and lowest heart rate in the ephedrine group was higher than those of control group. Also, there were significant lower incidences of hypotension and nausea and vomiting in the ephedrine group compared with the control group. The findings suggest the prophylactic bolus dose of 0.5 mg/kg intravenous ephedrine given at the time of intrathecal block after a crystalloid fluid preload, plus rescue boluses reduce the incidence of hypotension [86]. A similar randomized, double-blinded, controlled trial was conducted using propofol as anesthetic inducer (n = 156). Authors concluded that adding 30 mg of ephedrine to 20 ml of 1 % propofol is as effective as adding lidocaine in preventing injection pain, and it results in a more stable hemodynamic profile in the patients [87].

Ephedrine was first reported to be effective in the treatment of myasthenia gravis in the 1930s but was subsequently superseded by anticholinesterases and corticosteroids. The mechanism by which it may affect neuromuscular transmission at pharmacologic doses is unclear. Anecdotally, patients with congenital myasthenic syndrome (CMS) have reported benefit from ephedrine, often tried because of a failed response to other therapies. A study was conducted following 10 patients with Dok-7 mutation CMS. Dok-7 is an adaptor protein that is a key component of the muscle-specific tyrosine kinase (MuSK) signaling pathway and is essential for postsynaptic specialization of the neuromuscular junction. In this rare condition, the clinical phenotype is typically characterized by a definite onset of weakness in early childhood, although in retrospect symptoms consistent with a CMS may have been present at birth, sparing of the external ocular muscles in most cases, and a predominant limb–girdle distribution of weakness. A surprising feature of this form of CMS is the lack of response or worsening of weakness with anticholinesterase treatment and a variable response to 3,4-diaminopyridine (3,4-DAP), the conventional CMS treatments. This study provided Class IV evidence that ephedrine given at doses between 15 and 90 mg/day improves muscle strength and mobility in Dok-7 CMS [88].

A randomized, controlled, double-blind, clinical trial was conducted to assess the efficacy and safety of herbal extracts of *E. sinica* in Korean premenopausal women (n = 125). Subjects were administered ephedra extract in capsules

(pseudoephedrine 31.52 mg) or placebo capsules as well as participating in a low-calorie diet for 8 weeks. Ephedra combined with a low-calorie diet was effective in reducing body mass index [89].

7 Conclusion

Ephedrine is a classical sympathomimetic agent used for centuries in medicine. In spite of its natural origin, most of the commercial ephedrine comes from synthetic or semisynthetic processes. Nowadays, it is commonly used as a nasal decongestant and for weight loss and for recreational purposes. Furthermore, promising uses have been investigated, such as for the reduction of the incidence of hypotension during spinal anesthesia and for the treatment of some cases of myasthenic syndrome. In spite of the reports of serious adverse cardiovascular side effects attributed to ephedrine, it is a safe drug if correctly used. However, some attention has been given to the toxicity of the association of ephedrine with other stimulant compounds for weight-loss purposes.

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