CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Review Article

THERAPEUTIC IMPORTANCE OF EPHEDRA *ALATA* AND *EPHEDRA FOLIATA*- A REVIEW

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Received: 01 February2017 **Accepted:** 08 February 2017 **Published:** 28 February 2017

Abstract:
The preliminary phytochemical analysis of Ephedra alata indicated the presence of cardiac glycosides, reducing sugars, flavonoids, phenolic compounds and alkaloids. Ephedra species contain alkaloids ephedrine, pseudoephedrine, norephedrine, norpseudoephedrine, methylephedrine, and methylpseudoephedrine. Beside the E-type alkaloids, ephedroxane, and macrocyclic spermidines called ephedradine A-D, were isolated from some Ephedra species. The total amount of alkaloids isolated from Ephedra alata aerial parts was 0.2-0.22%. Phenolic compounds included chlorogenic acid, rutin, catechin, quercetin, coumaric acid, flavonoid (Vicenin II, lucenin III, kaempferol 3-rhamnoside, quercetin 3-rhamnoside, herbacetin 7-glucoside, herbacetin 8-methyl ether 3-O-glucoside-7-O-rutinoside and herbacetin 7-O-6"-quinylglucoside) and furanofuran ((±)-syringaresinol, digalloylglucose, nilocitin, p-coumaric acid) were isolated from Ephedra alata. Ephedra foliata also produced ephedrine and pseudoephedrine. The total alkaloids contents of Ephedra foliata (ephedrine and psudoephedrine) were 0.04-0.2%. Previous pharmacological studies revealed that Ephedra species possessed antimicrobial, antioxidant, antidiabetic, hepatoprotective and cardiovascular effects. This review discussed the chemical constituents and pharmacological effects of Ephedra alata and Ephedra foliata.

Keywords: *Ephedra alata, Ephedra foliata, pharmacology, constituents, therapy*

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*Please cite this article in press as Ali Esmail Al-Snafi, **Therapeutic Importance of Ephedra Alata And Ephedra Foliata- A Review**, Indo Am. J. P. Sci, 2017; 4(02).*

INTRODUCTION:

Herbal medicine is the oldest form of medicine known to mankind. It was the mainstay of many early civilizations and still the most widely practiced form of medicine in the world today. The World Health Organization (WHO) estimates that 4 billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care. Plant showed wide range of pharmacological activities including antimicrobial, antioxidant, anticancer, hypolipidemic, cardiovascular, central nervous, respiratory, immunological, anti-inflammatory, analgesic antipyretic and many other pharmacological effects [1-25]. The preliminary phytochemical analysis of *Ephedra alata* indicated the presence of cardiac glycosides, reducing sugars, flavonoids, phenolic compounds and alkaloids. Ephedra species contain alkaloids ephedrine, pseudoephedrine, norephedrine, norpseudoephedrine, methylephedrine, and methylpseudoephedrine. Beside the E-type alkaloids, ephedroxane, and macrocyclic spermidines called ephedradine A-D, were isolated from some *Ephedra* species. The total amount of alkaloids isolated from *Ephedra alata* aerial parts was 0.2-0.22%. Phenolic compounds included chlorogenic acid, rutin, catechin, quercetin, coumaric acid, flavonoid (Vicenin II, lucenin III, kaempferol 3-rhamnoside, quercetin 3-rhamnoside, herbacetin 7-glucoside, herbacetin 8-methyl ether 3-O- glucoside-7-O-rutinoside and herbacetin 7-O-6″-quinylglucoside) and furanofuran ((±)-syringaresinol, digalloylglucose, nilocitin, *p*-coumaric acid) were isolated from *Ephedra alata. Ephedra foliata* also produced ephedrine and pseudoephedrine. The total alkaloids contents of *Ephedra foliata* (ephedrine and psudoephedrine) were 0.04-0.2%. Previous pharmacological studies revealed that *Ephedra* species possessed antimicrobial, antioxidant, antidiabetic, hepatoprotective and cardiovascular effects. This paper will reviewed the chemical constituents and pharmacological effects of *Ephedra alata* and *Ephedra foliata.*

Synonyms:

***Ephedra alata*:**

Ephedra alata Decne. subspecies *alenda* Stapf, *Ephedra alata* Decne. subspecies *decaisnei* (Stapf) Maire, *Ephedra alata* Decne. subspecies *monjauzeana* Dubuis & Faurel and *Ephedra alenda* (Stapf) Andr [26].

Ephedra foliata:

*Ephedra aitchisonii (*Stapf*) V. A. Nikitin***,** *Ephedra alte* Brandis**,** *Ephedra alte* C. A. Mey.**,** *Ephedra asparagoides* Griff.**,** *Ephedra ciliata* Aitch.**,** *Ephedra ciliata* Fisch. *&* C. A. Mey.**,** *Ephedra ciliata var. polylepis* (Boiss. & Hausskn.*) Riedl***,** *Ephedra foliata var. aitchisonii* Stapf**,** *Ephedra foliata var. ciliata (*Fisch. & C. A. Mey.*)* Stapf**,** *Ephedra foliata var. polylepis* (Boiss. & Hausskn.) Stapf**,** *Ephedra kokanica* Regel**,** *Ephedra peduncularis* Boiss.**,** *Ephedra polylepis* Boiss. & Hausskn.**,** *Ephedra rollandii* Maire *[27].*

Taxonomic classification:

Kingdom: Plantae; **Phylum**: Tracheophyta; **Division:** Gnetophyta; **Class**: Gnetopsida; **Order**: Ephedrales; **Family**: Ephedraceae; **Genus**: *Ephedra*; **Species**: *Ephedra alata* and *Ephedra foliata* [28-29].

Common names:

***Ephedra alata*: Arabic:** Alanda, Alanda Mujanaa**;** Theel maiz, ephedra, Anab bahar, Ather, jashia**; English:** Ephedra.

Ephedra foliata: **Arabic:** Alanda warakia, fedr waraki, Al-Kuood al-waraki; **English**: Shrubby horsetail.

Distribution:

The genus is indigenous to the temperate and subtropical latitudes of Europe, Asia, and America, and grows especially in northern and western China, northern India, and Spain. In the United States, ephedra plants grow along the Rocky Mountains [30].

Ephedra alata: is distributed in Africa: Algeria; Egypt, Libyan, Morocco, Tunisia, Mauritania, Chad, Mali and in Asia: Saudi Arabia, Iraq, Iran, Palestine, Lebanon, Jordan and Syria [31].

***Ephedra foliata*:** is native to North Africa and Southwest Asia, it is distributed in Asia (Afghanistan, India, Punjab, Iran, Iraq, Jordan, Palestine, Kuwait, Qatar, Bahrain, Saudi Arabia, United Arab Emirates, Oman and Yemen) and in Africa (Chad, Algeria, Egypt, Mauritania, Morocco, Somalia, Djibouti and Ethiopia) [32-34].

Traditional uses:

The Chinese dispensatory written in 1569 mentions that *Ephedra* species were valuable as an antipyretic, diaphoretic, circulatory stimulant, and sedative for cough. However, *Ephedra* has been used in traditional Chinese medicine to treat allergies, asthma, lung congestion, chills, colds, hay fever, coughs, edema, fever, flu, headaches, and nasal congestion. The plant was also traditionally used in Russia for respiratory disorders and rheumatism for many centuries. The Native Americans and Spaniards of the southwestern United States used ephedra for various medicinal purposes, especially venereal diseases [25-26].

An active principle was first isolated by Yamanashi in 1885. In 1887, Nagai obtained the alkaloid in pure form and named it ephedrine. Pharmacological investigation

indicated that the drug was toxic, mydriatic and sympathomimetic [30].

Description:

Ephedra alata: is short, evergreen and almost leafless shrubs that grow about 60 to 90 cm high high. The stems are green in color, slender, erect or reclining, small ribbed and channeled, about 1.5 mm in diameter and usually terminating in a sharp point. Nodes are 4 to 6 cm apart, and small triangular leaves appear at the stem nodes . The nodes are characteristically reddish brown. The stems usually branch form the base. They bear minute, yellow-green flowers and fruits, and emit a strong pine-like odor and have an astringent taste [37-38].

Ephedra foliata: scandent or trailing plant. Branches slender. Leaves 2-4 at the upper nodes, 0.8-3.0 × 0.1 cm, linear. Male strobili solitary or 2-3 per node; flowers 4-6 pairs, bracteate; bracts connate, obtuse; anthers 3-4, sessile. Female strobili pedunculate, ovoid, 2-3-flowered. Tubillus c. 1.5 mm long, straight. Berry globose, white. Seeds 2, brownish-black [39].

Medicinal part: aerial parts, and mainly the stems of the plants [40-42].

Chemical constituents:

Ephedra alata:

The preliminary phytochemical analyses of *Ephedra alata* indicated the presence of cardiac glycosides, reducing sugars, flavonoids, phenolic compounds and alkaloids [43]. Ephedra species contain alkaloids ephedrine, pseudoephedrine, norephedrine, norpseudoephedrine, methylephedrine, and methyl pseudoephedrine. Beside the E-type alkaloids, ephedroxane, and macrocyclic spermidines called ephedradine A-D, which isolated from some Eurasian Ephedra species [44]. The total amount of alkaloids isolated from *Ephedra alata* aerial parts was 0.2-0.22% [41].

The amount of ephedrine in *Ephedra alata* was 0.05–0.19%, pseudoephedrine > 0.5%, while the amount of tannin was 0.2–0.5% [45].

To develop a protocol for callus induction and ephedrine production from the stem of *Ephedra alata*. The highest callus induction and fresh weight of callus were shown on Murashige and Skoog medium supplemented with 1 mg/l of both 2,4-dichlorophenoxyacetic acid (2,4-D) and kinetin. The maximum ephedrine obtained from callus reached 14.06 mg/g dry weight and exceeded the ephedrine content in the stem of both wild and cultivated intact plants. Feeding the culture medium with different concentrations of L-phenylalanine, as a precursor, or casein hydrolysate, as an elicitor, did not increase the ephedrine accumulation in callus cultures [40].

Phenolic compounds included chlorogenic acid, rutin, catechin, quercetin, coumaric acid were obtained from callus of *Ephedra alata* maintained in the media containing casein hydrolysate [46].

Flavonoid isolated from *Ephedra alata* were included Vicenin II, lucenin III, kaempferol 3-rhamnoside, quercetin 3-rhamnoside, herbacetin 7-glucoside, herbacetin 8-methyl ether 3-O- glucoside-7-O-rutinoside and herbacetin 7-O-(6″-quinylglucoside [47].

Total flavonoid contents of *Ephedra alata* were determined by using rutin reference standard method and total phenols were determined by using Folin Ciocalteu method. The total phenolic content was highest in the methanolic extract (47.62 mg gallic acid equivalent/g of extract powder) , while in ethanolic extract, the total phenolic content was 19.175 mg gallic acid equivalent/g of extract powder. The total flavonoid content of the plant was 0.519 mg rutin /g in the aqueous extract and 5.44 mg RU/g in the ethanolic extract while was the highest in the methanolic extract 54.66 mg rutin /g [43].

However, Ibragic *et al*., found that the total phenolics contents in *Ephedra alata* was 53.3±0.1 mg Gallic acid equivalents/g dry weight and total flavonoids contents was 28.0± 0.0 mg/g dry weight [48].

Furanofuran lignan (±)-syringaresinol, digalloylglucose, nilocitin, *p*-coumaric acid and a new natural alkaloid, ephedralone were obtained from the *Ephedra alata* [36].

Many acids including : 2-propenoic acid, 3-phenyl (18.19%), benzoic acid (7.60%), 2-propenoic acid, 3-phenyl- methy, (2.17%), benzene- acetic acid, alpha.-hydrox (1.43%), benzene - dicarboxylic acid, diis 1.2-(1.41%), hexadecanoic acid - (1.21%), benzoic acid 4-hydroxy, acid ethyl ester (1.17%) and benzene - propanoic acid (1.15%), were isolated from dichloromethane extract of *Ephedra alata* leaves [49].

The dichloromethane extracts of aerial parts from *Ephedra alata* afford 52 compounds in leaves and 65 compounds in flowers. The main compounds of the leaves are: 2-propenoic acid, 3-phenyl (18.194%); phenol, 4-(3-hydroxy-1- propenyl) (7.881%), benzoic acid (8.521%), benzaldehyde, 4-hydroxy-3,5-dimethyl (7.036%); benzaldehyde, 4-hydroxy- 3-methoxy (4.381%). On the other hand the flowers contain some important compounds such as benzoic acid (16.874%), 2- propenoic acid , 3- phenyl (11.453%), 1,2-benzenedicarboxylic acid, diis (5.112%), benzenemethanol (3.675%) and benzeneethanol (3.645%) [50].

***Ephedra foliata*:**

Ephedra foliata also produced ephedrine and pseudoephedrine [51-52]. The total alkaloids contents

of *Ephedra foliata* (ephedrine and Psudoephedrine) were 0.04-0.2% [53].
Ephedra foliata callus produce 0.1% ephedrine and pseudoephedrine under white light, an attempt to induced *Ephedra foliata* callus to produce elevated quantities of ephedrine and pseudoephedrine, it appeared that culture tissues subjected to blue or red light, increased the production threefolds [54].
Ephedrine and pseudoephedrine were reacted with nitrite under physiological conditions (37 degrees C, pH 1-3) to form N-Nitrosoephedrine (NEP) and N-nitroso pseudo ephedrine (NPEP). Aqueous and alcoholic extracts of *Ephedra foliat*a (100 g dry wt), nitrosated under physiological conditions, produced 0.77 mg and 8.3 mg of NEP and NPEP, respectively [55].
Total phenolics contents, and total flavonoids contents were estimated in *Ephedra foliata*. Total phenolics contents was 52.6±0.1 mg Gallic acid equivalents/g dry weight and total flavonoids contents was 25.0± 0.0 mg/g dry weight [48].

Pharmacological effects:
Antimicrobial effects:
The antimicrobial activity of different extracts of *Ephedra alata* stem was investigated against bacteria, yeast and fungi. Four bacteria, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Escherichia coli* and four fungi, *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, and *Candida albicans* were used as test microorganisms. Acetonitrile extracts exhibited the most potent antimicrobial effect with a broad spectral range. Thin layer chromatographic separation of active constituents in acetonitrile extracts revealed the presence of seven fractions. All fractions showed antimicrobial activities with four fractions having a potent inhibitory effect [42].
The antibacterial activity of of flavonoid extracts of *Ephedra alata* was evaluated against Gram positive and Gram negative pathogenic bacteria (*Serratia marcescens* ATCC 13880, *Pseudomonas aeruginosa* ATCC 10145, *Bacillus subtilis* ATCC 6051, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 11778, *Methicillin -resistant Staphylococcus aureus (MRSA)* ATCC 013300 and *Staphylococcus aureus* ATCC 29213). The results exhibited variable susceptibilities of microorganisms. The activity was associated with high concentration. The extracts of *Ephedra alata* displayed relatively important effects with a variable diameter of growth inhibition zones in most types of bacteria. However no effect was recorded against *Serratia marcescens* ATCC 13880 with butanol extracts of flowers and leaves and ethyl acetate and dichloromethane extracts of leaves. Butanol, ethyl acetate, and dichloromethane extracts of leaves showed no activity against *Enterococcus faecalis* ATCC 29212 [56].
The aqueous extract of *Ephedra alata* had significant inhibitory potential against growth as well as aflatoxin production by aflatoxigenic seedborne mold (*Aspergillus flavus*). Moreover, it has been found that, the addition of 1 and 2% (w/w) of plant powder material of *Ephedra alata* to corn grains and soybean seeds respectively decreased the aflatoxin contamination and improve their nutritional value (total nitrogen content, fiber content, total lipids content and ash content) under storage conditions [57].
The use of *Ephedra alata* extracts significantly decreased the total lipid, sterols, neutral lipids, phospholipids and fatty acid content of *Aspergillus flavus*. These effects could be represented the mechanism of antifungal activities of *E. alata* [58].

Antioxidant effect:
The antioxidant activity of *Ephedra alata* was evaluated by 2, 2-diphenyl-1-picryl-hydrazyl-hydrate assay. *Ephedra alata* methanolic extract showed high antioxidant activity and powerful oxygen free radical scavenging abilities, the IC_{50} for the plant was almost equivalent to the Trolox standard antioxidant [43].

Hypoglycemic effect:
Alcoholic extract of *Ephedra alata* exerted hypoglycemia, one hour after administration to fasting rats. The same extract failed to reduce blood glucose levels in alloxanized rats compared to the positive control, glibenclamide [59].

Hepatroprotective effect:
The hepatroprotective effect of *Ephedra foliata* was studied in Wistar albino rats. Liver injury was induced in rats using carbon tetrachloride. The biochemical parameters; serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP) and total bilirubin were estimated as reflection of the liver condition. The hepatoprotective effect offered by *Ephedra foliata* (whole plant) crude extract at 500 mg/kg doses, was found to be significant in all parameters studied with 42.6, 39.5, 21.2 and 46.2% reduction in SGOT, SGPT, ALP and bilirubin, respectively. At the lower doses (250 mg/kg) the extract resulted in a significant reduction in SGOT, ALP and bilirubin ($P< 0.05$) [60].

Pharmacology of Ephedrine:
Ephedrine stimulated both α and β receptors. This effect was partly by a direct action on the receptors and partly indirectly by releasing noradrenaline from its tissue stores, the effect of the ephedrine in various organs and systems was similar to that of adrenaline. It is also a

mild CNS stimulant. As general, it produced the following pharmacological effects:

1-Cardiovascular effects:

The effect of ephedrine administered intravenously to experimental animals was similar to that of epinephrine. The arterial pressure, systolic, diastolic, and mean pressure rised and vagal slowing occured. In comparison with epinephrine, the pressor response to ephedrine occured somewhat more slowly and lasted about ten times longer. In addition, it required more ephedrine than epinephrine to obtain an equivalent pressor response. It was commonly accepted that it required about 250 times more ephedrine than epinephrine to achieve equipressor responses. The pressor response to ephedrine is due in part to peripheral constriction and in part to myocardial stimulation. Vasoconstriction can be demonstrated by intra-arterial injection, but compared to epinephrine, ephedrine was only about one thousandth as active. This would imply that the cardiac effect was predominant in increasing the arterial pressure. In humans, ephedrine increases the arterial pressure both by peripheral vasoconstriction and by cardiac stimulation. The heart rate was usually increased, as was the pulse pressure, both suggesting an increased cardiac output. However, the hypotension that commonly occured during surgery under spinal anesthesia was practically always prevented by ephedrine. As a conclusion, it appeared that ephedrine activated the same adrenergic receptors as epinephrine but was less potent and has a longer duration of action. In complete heart block with Stokes–Adams syncope, ephedrine proved of value to increase ventricular rate and prevent ventricular asystole, an initial dose of about 8 mg of ephedrine sulfate orally may be tried, then the dose increased to 25 mg three or four times daily. Syncope due to ventricular tachycardia can also be prevented in some cases with ephedrine [30, 61].

2. Bronchodilitation:

The smooth muscle of the bronchial tree was relaxed by ephedrine. Compared with epinephrine, the action of ephedrine was slow in onset, completed an hour or more after administration. Ephedrine also prevented histamine-induced broncho-constriction in patients with asthma [30].

3. Nasal decongestion:

Because of vasoconstrictive effect of ephedrine, it was utilized as a decongestant solutions applied topically to the mucous membranes of the nose. Similar to epinephrine, ephedrine often produced a secondary congestive response [30, 61].

4. Mydriasis:

Ephedrine produced mydriasis when applied locally to the conjunctiva, as well as upon systemic absorption.

5. Nocturnal enuresis:

Ephedrine hydrochloride tablets were used in many trials to control nocturnal enuresis. It was appeared that ephedrine hydrochloride improved internal sphincter tone, thus preventing uncontrolled urination [51-63].

6-Spinal anesthesia:

Ephedrine was used to prevent occurance of hypotension during surgery under spinal anesthesia. The usual dose of ephedrine employed to treat, rather than prevent, the hypotension was 50 mg intramuscularly or 15 mg intravenously. The central stimulant action of ephedrine, which may be objectionable, was controlled by adequate preanesthetic sedation or the concomitant use of a short acting Barbiturate [30].

7-CNS stimulation

Ephedrine was a corticomedullary stimulants. Depending on the dose, this stimulant action in humans results in feelings of anxiety, tremor, insomnia and mental alertness, and increased respiration. When ephedrine was used for its adrenergic effects, the central stimulation was considered as a side effect. However, ephedrine was used previously as a useful central stimulant in narcolepsy and depressant poisoning, but amphetamine and methamphetamine were commonly used today [30].

8- Weight lost:

Today, *Ephedra* was applicated for enhancing performance, appetite suppression and weight lost [64]. Several studies have found that ephedrine/caffeine combinations were modestly effective for short- and long-term weight loss [65-68]. Furthermore, ephedrine stimulant effect caused an increase in basal metabolic rate that contributes to weight loss [69].

9- Cytotoxic effects of ephedrine and pseudoephedrine:

Cytotoxicity of (-)-ephedrine and (+)-pseudoephedrine was examined against two different cell lines , SH-SY5Y and H9c2 (2-1) cells. By both, the percentage of viable cells decreased significantly in a dose dependent manner. For SH-SY5Y, the IC50 value of (-)-ephedrine was 0.619 ± 0.004 mg/ml and (+)-pseudoephedrine was 0.605 ± 0.011 mg/ml. For H9c2 (2-1), the IC50 value of (-)-ephedrine was 0.617 ± 0.005 mg/ml and (+)-pseudoephedrine was 0.666 ± 0.012 mg/ml. The IC50 value of (-)-ephedrine to H9c2 (2-1) was significantly lower than that of (+)-pseudoephedrine ($P< 0.01$). As the concentration of (-)-ephedrine increases, swelling of the cells became prominent and vacuolar degeneration was observed microscopically [38].

10- Other effects:

Ephedrine produced the same effects of epinephrine on smooth muscle. It inhibited the contraction of intact gastrointestinal musculature and stimulated contraction of the splenic capsule and pilomotor muscles. It possessed the same myometrial and urinary bladder actions as epinephrine. Ephedrine also produced

hyperglycemia and eosinopenia. Ephedrine influenced the muscular weakness of myasthenia gravis favorably by unknown mechanism. Isolated skeletal muscle was contracted by ephedrine, the observed effect was not depended on the actions of ephedrine on vascular system or CNS. Secretions of the gastrointestinal tract were inhibited by ephedrine. Ephedrine also decreased the output of pancreatic juice [30].

Ephedrine kinetics:

Ephedrine in absorbed from the gastrointestinal tract and from all parenteral sites. It characterized by good distribution throughout the body and was resistant to hydrolysis by the liver enzymes. Major proportion of the drug was excreted unchanged in the urine. Because of its stability to metabolism it characterized by long duration of action than the catecholamines [61].

Side effects, toxicicity and contraindications:

Unlike most other herbal drugs, Ephedra carry a health risk, which aggravated by their misuse and/or abuse. According to the Food and Drug Administration (FDA) assessment in 2004, food supplements containing Ephedra alkaloids represented an unacceptable health risk. FDA banned all over the counter drugs containing ephedrine. Many adverse cardiovascular and cerebrovascular events were associated with the use of dietary supplement preparations containing Ephedra alkaloids [70].

During two years 1993-1995, the Bureau of Food and Drug Safety, Texas Department of Health (TDH), received approximately 500 reports of adverse events in persons who consumed dietary supplement products containing ephedrine and associated alkaloids (pseudoephedrine, norephedrine, and N-methyl ephedrine). These reports recorded adverse events ranged in severity from tremor and headache to death in eight ephedrine users and included reports of stroke, myocardial infarction, chest pain, seizures, insomnia, nausea and vomiting, fatigue, and dizziness. Seven of the eight reported fatalities were attributed to myocardial infarction or cerebrovascular accident [71].

However, the side effects recorded with toxic doses of ephedrine were included convulsions, nausea, vomiting, chills, cyanosis, irritability, nervousness, fever, suicidal behavior, tachycardia, dilated pupils, blurred vision, opisthotonos, spasms, pulmonary edema, gasping respirations, coma, respiratory failure and personality changes [30, 72].

Ephedra should not be used in patients with coronary thrombosis, diabetes, glaucoma, heart disease, hypertension, thyroid disease, impaired circulation of the cerebrum, phaeochromocytoma, or prostate hyperplasia [73-74].

CONCLUSION:

The alkaloids of *Ephedra alata* and *Ephedra foliata* were used in medical practice for many decades, The current review discuss the chemical constituents and pharmacological effects of *Ephedra alata* and *Ephedra foliata* to encourage the uses of these species for other purposes.

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