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REVIEW

Medicinal and Therapeutic Properties of *Ephedra*

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Abstract

Ephedra is one of the oldest medicinal plants in traditional Chinese medicine for nearly 5000 years. The medicinal species are used as a stimulant and as antiasthmatic agents to treat cold, bronchial asthma, cough, fever, flu, headache, edema, and allergies. The medicinal and therapeutic effects of these plants are related to alkaloids such as ephedrine, pseudoephedrine, norephedrine, and methylephedrine, and it also contains tannins and flavonoids. The most common compounds found in *Ephedra* are ephedrine and pseudoephedrine. Furthermore, a vast diversity of alkaloid and non-alkaloid compounds have been known in different species of *Ephedra*. In this study, a systematic search was performed to provide animal and clinical evidence regarding the therapeutic effects of the *Ephedra* herb. The purpose of this review is to describe the medicinal and therapeutic effects of *Ephedra* herb and their compositions.

Keywords Bioactive compounds · Phytochemicals · Antimicrobial · Antioxidant · Anti-asthma

Introduction

The Ephedraceae family has only one genus named *Ephedra* L., which has about 50 species worldwide (Pirbalouti et al. 2013; Mellado et al. 2019). The *Ephedra* family is native to the temperate and subtropical areas of Asia, Europe, Central, and North America (Elhadef et al. 2020). It is a perennial herbaceous plant that is more than 1 m high and has a strong pine odor and an astringent taste. A vast diversity of alkaloid and non-alkaloid compounds have been found in different species of *Ephedra* (González-Juárez et al. 2020). The plant has a mixture of alkaloids, including ephedrine, pseudoephedrine, norephedrine, and methylephedrine (Ibragic and Sofić 2015; Morris et al. 2018; Hung et al. 2021). They are the sources of thermogenic and stimulant agents such as (−) ephedrine (Stohs and Badmaev 2016). Their thermogenic effects cause a rise in metabolism, as evidenced by a rise in body heat. These materials stimulate the brain, rise heart rate, contract blood vessels (increasing blood pressure), and make breathing easier (Bents and Marsh 2007).

Ephedra species also contains tannins and flavonoids (Al-Awaida et al. 2018). Flavonoids are also an important class of secondary metabolites in the genus *Ephedra*. More than 40 flavonoids have been recognized from these species that are classified as flavonols, flavonones, flavones, flavanols, dihydroflavonols, and anthocyans. Flavones and their glycosides, such as flavonols and their 3-*O*-glycosides components, are the most usual flavonoids in genus *Ephedra* (Zhang et al. 2018). Tannins are also main constituents in this genus that mostly exist in the concentrate form. Tannins, mostly proanthocyanidins, have been demonstrated to be present in all *Ephedra* plants (Zang et al. 2013).

Ephedra is a medicinal plant used in Chinese medicine for thousands of years (Fan et al. 2015). Among all species, 15 species and four varieties grow in China. *Ephedra sinica* Stapf. is the early species that has been applied in China for more than 5000 years (Xie et al. 2013; Zhang et al. 2018). *Ephedra* has also different names in different regions, namely in Chinese “Ma Huang”; in Indian “Soma” (Joshi and Deokule 2019); in the English language “joint pine,” “Jointfir,” “sea grape,” “Mormon tea,” or “shrubby horsetails”; in French “raisin de mer”; and in Persian, “Ormak,

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Rish Boz, and Alijonak" (Pirbalouti et al. 2013). It has been used in Chinese medicine for many years to treat fever, chills, coughs, colds, asthma, headaches, flu, and edema (Bagheri-Gavkosh et al. 2009; Parsaeimehr et al. 2010; Solanki et al. 2014; Ojeda-Montes et al. 2017). Modern pharmacological research has evaluated many medicinal and therapeutic properties of various *Ephedra* species, which discussed below. The present review described the recent knowledge about novel applications of different species of *Ephedra* and their medical potential.

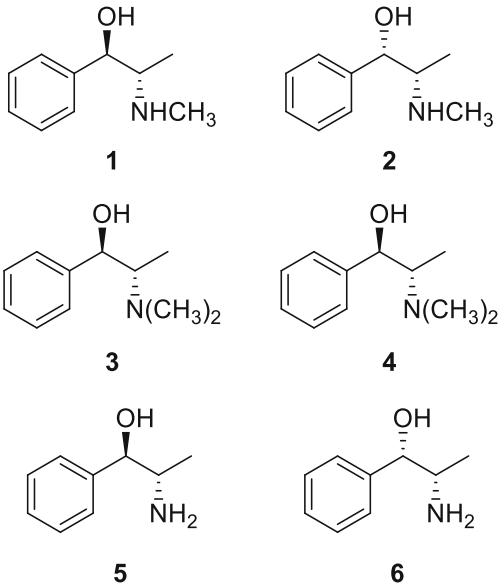
Search Strategy

The search for these works was performed using Web of Science, PubMed, Scopus, and Google Scholar databases, and "*Ephedra*" as keywords. In the present study, the search terms related to studies the existing animal and clinical evidence regarding the therapeutic effects of *Ephedra* herb and its possible mechanism were consulted.

Discussion

Chemical Content

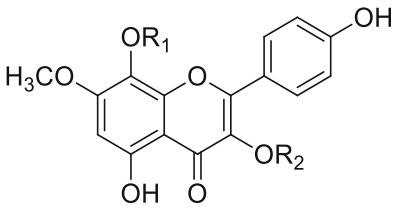
Ephedra species contain several alkaloids, including the major bioactive (−)-ephedrine (**1**), (+)-pseudoephedrine (**2**), (−)-(*N*-)-methylephedrine (**3**), (+)-(*N*)-methylpseudoephedrine (**4**), (−)-nor-pseudoephedrine (**5**), and (+)-norpseudoephedrine (**6**). Ephedrine was firstly isolated in 1885 and came into commercial use in 1926. It is on the World Health Organization's List of Essential Medicines. It is available as a generic medication. It can normally be found in plants of the *Ephedra* genus. Dietary supplements containing ephedrine are illegal in the USA, with the exception of those used in traditional Chinese medicine, where its presence is noted by *máhuáng* or *E. sinica* (up to 3.4% dry weight of alkaloids), which is native to China and the first commercial source of *Ephedra* alkaloids. The total alkaloid content in *E. monosperma* J.G.Gmel. ex C.A.Mey. and *E. equisetina* Bunge species is 2.5% and in *E. major* Host, *E. distachya* L., and *E. gerardiana* Wall ex Stapf. is 1 to 2% of the plant's dry weight. Ephedrine (**1**) belongs to a class of drugs called alpha/beta adrenergic agonists and is a prescription medicine used to treat the symptoms of low blood pressure during anesthesia (hypotension). Ephedrine may be used alone or with other medications.



Ephedrine occurs as fine, white, odorless crystals or powder and darkens on exposure to light. It is freely soluble in water and sparingly soluble in alcohol. Ephedrine sulfate, $(C_{10}H_{15}NO)_2{\cdot}H_2SO_4$, is a sterile solution of 50-mg ephedrine sulfate in water for injection and its chemical name is benzenemethanol α-[1-(methylamino) ethyl]-sulfate (2:1) (salt). Ephedrine sulfate injection is indicated in the treatment of allergic disorders, such as bronchial asthma. The drug has long been used as a vasopressor agent, particularly during spinal anesthesia when hypotension frequently occurs. In Stokes-Adams syndrome with complete heart block, ephedrine has a value similar to that of epinephrine (adrenaline A). It is indicated as a central nervous system stimulant in narcolepsy and depressive states. It is also used in myasthenia gravis, a chronic autoimmune disorder in which antibodies destroy the communication between nerves and muscle, resulting in weakness of the skeletal muscles. For adults, the usual parenteral dose is 25 to 50 mg given subcutaneously or intramuscularly. Intravenously, 5 to 25 mg may be administered slowly, repeated in 5 to 10 min, if necessary. In children, the usual subcutaneous or intramuscular dose is 0.5 mg/kg of body weight or 16.7 mg/m^2 of body surface every 4 to 6 h (Statler et al. 2021).

In addition to alkaloids, other types of secondary metabolites such as flavonoids, flavonols, tannins, carboxylic acids, and volatile terpenes have been reported in this plant. Flavonoids are aromatic compounds and, main components of *Ephedra* herbs, approximately 0.29% mass of this plant are flavonoids, flavanols, dihydroflavonols, dihydroflavonoids, flavonols, and anthocyanins (Shuang-Man et al. 2020). Recently, three new flavonoids, ephedroside A (**7**), ephedroside B (**8**), ephedroside C (**9**), together with fifty-four known compounds, were isolated from the

EtOH extract of the herbaceous stems of *E. sinica* (Duan et al. 2021). The phytochemical study of *E. viridis* Coville leads to the isolation and identification of four compounds of 9-acetoxylariciresinol, isolariciresinol, lariciresinol, and 9-acetoxyisolariciresinol (González-Juárez et al. 2020).

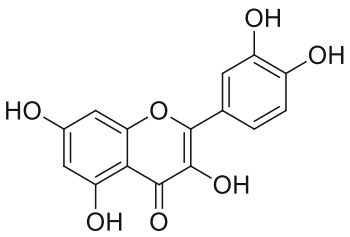


7 R_1=H; R_2=β-rutinosyl
8 R_1=H; R_3=β-mannopyranosyl
9 R_1=β-glucopyranosyl; R_2=H

Tannins, mainly proanthocyanidines, are mostly shown as dimers, trimmers, and tetramers, and often they are composed of catechin and epigallocatechin (Shuang-Man et al. 2020). Tannins are constituents of many *Ephedra* species in North American species including *E. nevadensis*, *E. californica*, *E. viridis*, *E. fasciculata*, *E. trifurca*, and *E. torreyana*, and Eurasian species including *E. intermedia*, *E. przewalskii*, *E. alata*, *E. distachya*, and *E. fragilis* (Ibragic and Sofić 2015). Up to date, 27 carboxylic acids have been isolated from various *Ephedra* species.

Ephedra herbs include approximately 0.15% of volatile organic compound. More than 200 kinds of volatile oils have been extracted from *Ephedra* species mostly including terpenes and alcohols (Shuang-Man et al. 2020). According to various studies, volatile oils reported in different species of *Ephedra* are mainly terpenoids (Miyazawa et al. 1997; Tellez et al. 2004; Vickers 2017).

For quantitative measurement in quality control of *Ephedra* herbs, gallic acid, as quercetin (**10**) or catechin (**11**) equivalents, and cyanidin-3-glucoside (chrysanthemin, **12**) were used as standard compounds to quantify total polyphenol, total flavonoid, and total anthocyanins content, respectively (Elhadef et al. 2020).



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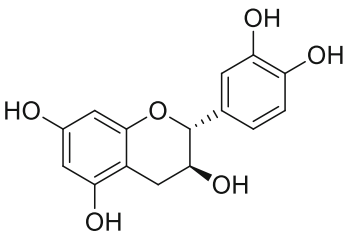

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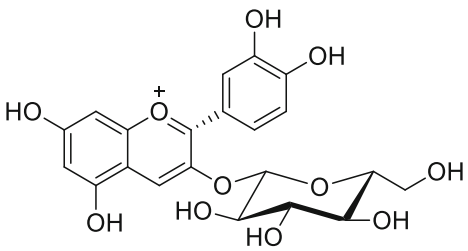

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Recently, the high-performance liquid chromatography (HPLC) and mass spectrometry (MS) were used widely to identify and quantify phenolic compounds from extracts of different *Ephedra* species. Elhadef et al. (2020) detected individual polyphenols (such as gallic acid, protocatechuic acid, caffeic acid, coumaric acid, ferulic acid, rosmarinic acid, epicatechin, rutin, resveratrol, quercetin, and kaempferol) of the hydroalcoholic extract of Tunisian *E. alata* by LC-MS. Additionally, vinyl guaiacol, syringol, di-tert-butylphenol, antiarol, and vitamin E of aqueous and methanolic extracts of *E. foeminea* were identified by HPLC-MS/MS (González-Juárez et al. 2020). Benabderrahim et al. (2019) determined levels of epicatechin, quinic acid, rutin, *p*-coumaric acid, cirsilineol, and luteolin in Tunisian *E. alata* ethanolic extract by liquid chromatography-electrospray ionization–tandem mass spectrometry. Using HPLC coupled to photodiode array and electrospray ionization mass spectrometric method, Mighri et al. (2019) detected 24 phenolic compounds in the hydromethanolic extract of *E. alata* crude. These compounds were 10 phenolic acids (protocatechuic acid, quinic acid, 4-*O*-caffeoylquinic acid, *trans*-ferulic acid, syringic acid, caffeic acid, *p*-coumaric acid, chlorogenic acid, *trans*-cinnamic acid and gallic acid), 5 flavones (cirsiliol, apigenin, cirsilineol, acacetin and luteolin), 2 flavonol glycosides (quercitrin and rutin), 2 flavan-3-ols (epicatechin and (+)-catechin), 2 flavone glycosides (apigenin-7-*O*-glucoside and naringin), 2 flavonols (kaempferol and quercetin), and 1 flavanone (naringenin) .Ibragic and Sofić (2015) used dry herbs of *E. altissima*, *E. foeminea*, *E. distachya* subsp. Helvetica, *E. alata*, *E. foliate*, *E. monosperma*, *E. fragilis*, and *E. major*

for separating and quantifying ephedrine and pseudoephedrine using ultra high-pressure liquid chromatography coupled to a UV detector.

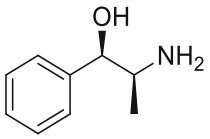
Therapeutic Properties

The family of Ephedraceae has been reported to possess medicinal and therapeutic properties as nutritional supplements, stimulants of the central nervous system, and antimicrobial activity, *inter alia* (Fig. 1 and Table S1).

Nutritional Supplements

In the West, many people use *E. sinica*, *E. intermedia*, and *E. equisetina* in dietary supplements as a weight-loss stimulant (Xia et al. 2011; Additives et al. 2013). Ephedrine is the strongest thermogenic agent of the *Ephedra* plant alkaloids. Ephedra alkaloids have been used, as supplements by athletes with their stimulating properties and sympathomimetic actions as products that can enhance athletic performance (Avois et al. 2006). Ephedrine (**1**) increases energy consumption by increasing thermogenesis and thereby reducing weight. The thermogenic effects of ephedrine are due to stimulation of peripheral β receptors (Jeon 2011).

Research has demonstrated that the use of ephedrine (**1**), pseudoephedrine (**2**), and phenylpropanolamine (**13**), isolated from the *Ephedra*, alone at usual dosages of three servings of 20 to 25 mg of ephedrine per day, has an inconsistent and probably has little ergogenic benefits in strength, speed, ability, and stability (Avois et al. 2006). In general, many athletes are taking supplements containing *Ephedra* alkaloids because of the benefits of increased energy, reduced fatigue time, thermogenic properties, reduced fat, and strengthen muscles (Avois et al. 2006).



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Greenway et al. (2004) investigated the effect of a dietary herbal supplement containing *Ephedra* and caffeine on body composition, weight, and metabolic rate. The steps of this study are performed in three phases and efficiently reduce body weight and fat which were shown with the consumption of 210 mg caffeine and 72 mg *Ephedra* per day for 12 weeks with improvement in lipid metabolism and blood pressure without serious adverse effects.

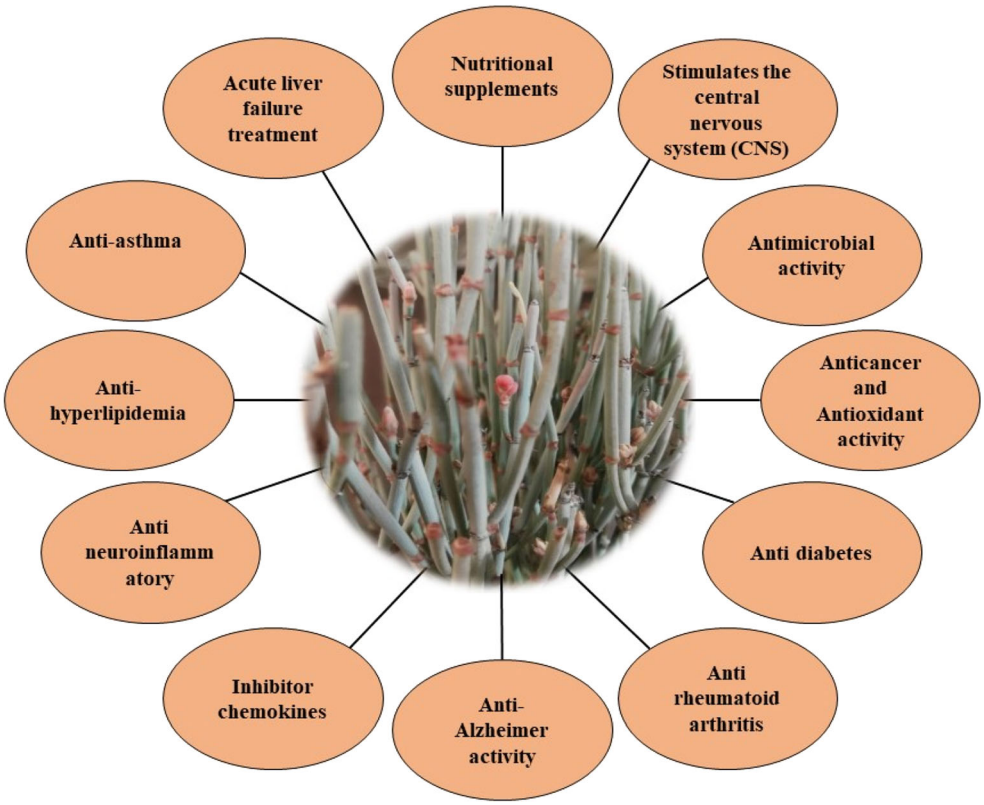


Fig. 1 Medicinal and therapeutic properties of *Ephedra*

In a human clinical trial, Boozer et al. (2001) examined in obese humans the short-term safety and effectiveness for weight loss of a herbal supplement containing *Ephedra*, guarana (*Paullinia cupana* Kunth, Sapindaceae), and other ingredients. This study performed on 67 people (two groups of placebo, 32 people, and active ephedra-guarana, 35 people) in 8 weeks double-blind placebo-controlled, randomized study by a herbal dietary supplement including 72 mg/day ephedrine alkaloids and 240 mg/day caffeine (Boozer et al. 2001). The results of this study showed a significant reduction in body weight in the test group (−4.0 ± 3.4 kg or 3.5% of baseline) compared with the placebo group (−0.8 ± 2.4 kg or 0.09% of baseline) (Boozer et al. 2001). The safety and efficacy of herbal medicines were investigated in the treatment of obesity that included 77 studies (19 human and 58 animal studies). The results revealed that *Ephedra* is one of the herbs that significantly decrease body weight (Hasani-Ranjbar et al. 2009).

According to WHO statistics, the average life expectancy of women in most countries is approximately 80 years. The majority of women will reach menopause, both naturally and surgically. About 55 and 75% of these women will experience vasomotor symptoms (hot flashes) or different symptoms, such as sleep disorders, mood swings, depression, vaginal dryness, and joint injury. In many cases, hormone replacement therapy was recommended as the first-line treatment during menopausal signs (Grodstein et al. 1997). Mahady et al. (2003) investigated the utilization of botanical dietary supplement (BDS) on females between the ages of 40–60. In this study, 500 women outpatients at the University of Illinois at Chicago clinics were interviewed using a botanical/drug history questionnaire. BDS was consumed by 395 people (79%) of respondents, of which 36.5% consumed BDS daily. The decoction of *Ephedra* was consumed by less than 15% of respondents and has been reported to be effective as a supplement during peri- and postmenopausal. The effects of oral *Ephedra* decoction were studied on hormone level in ovariectomized obese rats, where forty-four healthy female Sprague Dawley rats were randomly divided in 4 groups (11 rats in each group), namely sham-operated group, ovariectomized group, *Ephedra* group, and estrogen replacement treatment group. Rats underwent a bilateral ovariectomy excluding those in the sham-operated group that were also operated, but their ovaries were not cut. The rats in the *Ephedra* group freely drank 1% aqueous extracts of *Ephedra* postoperatively; subsequently, the concentration from *Ephedra* gradually raised to 8% in the sixth day, which continued to the end of the test. After measuring serum levels of estrogen and progesterone, it was demonstrated that *Ephedra* could promote the serum levels of hormones in the *Ephedra* group (Yue et al. 2007).

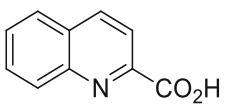
Stimulants of the Central Nervous System

Ephedrine (**1**), pseudoephedrine (**2**), and phenylethylamine are substances that have stimulatory effects on the central nervous system (CNS), in a similar way with amphetamines that act on central adrenaline receptors of α and β (Brown et al. 2012; Głowacka and Wiela-Hojeńska 2021). Ephedrine raises the release of noradrenaline that reduces food uptake, and functions as a sympathomimetic factor to stimulate blood pressure and heart rate and increase thermogenesis (Stohs and Badmaev 2016). Ephedrine is close to amphetamine-type derivatives that include psychedelics, stimulants, and entactogens, and also anorectics, bronchodilators, decongestants, and antidepressants (Carvalho et al. 2012; Limberger et al. 2013).

Antimicrobial Activity

Gastric ulcer is one of the most critical gastrointestinal disorders. One of the most important causes of gastric ulcer is *Helicobacter pylori*. Pirbalouti et al. (2013) showed that omeprazole and hydro-alcoholic extract of *E. pachyclada* at concentrations of 500 and 100 mg/kg indicated 99.8%, 100%, and 100% healing effect on gastrointestinal ulcers, respectively. Moreover, they proved the anti-ulcer effect and proposed that it may be due to the antioxidant mechanism of action.

Ephedra also affected intestinal bacteria. The methanolic extract of *E. pachyclada* at concentration of 1 mg/ml inhibited the growth of intestinal Gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumonia*, *Serratia marcescens*, and *Shigella dysentery*. However, *Pseudomonas aeruginosa* was inhibited at a concentration of 0.5 mg/ml (Sadeghi Dosari et al. 2016). In another study, Lee and Lee (2009) examined the antibacterial activity of *E. pachyclada* on another group of intestinal bacteria including *Clostridium difficile*, *Clostridium perfringens*, *Lactobacillus acidophilus*, and *Lactobacillus casei*. Purification of the active component of *E. pachyclada* stems conducted with HPLC yields the structure of the active constituent, recognized as quinaldic acid or quinoline-2-carboxylic acid (**14**), which exhibited a potent inhibition at 1 mg/disk against *C. perfringens* and *C. difficile*, and moderately inhibited the growth of *C. perfringens* and *C. difficile* at 0.1 mg/disk and 0.5 mg/disk, respectively, but had no effect on *L. acidophilus*, *Bifidobacterium bifidum*, and *L. casei.*



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Ziani et al. (2019) examined the effect of hydroethanolic extract of *E. alata* Decne. on ten clinical bacteria, including

four Gram-positive (*Enterococcus faecalis*, *Listeria monocytogenes*, methicillin-resistant *Staphylococcus aureus*, and methicillin-sensitive *S. aureus*) and six Gram-negative (extended-spectrum beta-lactamase–producing *E. coli*, *K. pneumoniae*, *Morganella morgani*, and *P. aeruginosa*), with minimum inhibitory concentration (MIC) ranging from 5 to 10 mg/ml. Antimicrobial activity of *E. alata* plant examined against four bacteria of *P. aeruginosa*, *S. aureus*, *E. coli*, and *Bacillus subtilis* and four fungi including *Penicillium italicum*, *Aspergillus fumigatus*, *Syncephalastrum racemosum*, and *Candida albicans* (Ghanem and El-Magly 2008). Thin-layer chromatography applied for the separation of active components, and between all solvents tested, acetonitrile extracts showed the strongest antimicrobial efficacy with a wide spectral range. *E. alata* extract showed high activity against both fungi and Gram-positive and Gram-negative bacteria. Furthermore, *A. fumigatus* was the most sensitive fungal strain to acetonitrile extract even at low concentrations (Ghanem and El-Magly 2008).

The antibacterial and antifungal activity of three species of *E. strobiliacea*, *E. procera*, and *E. pachyclada* on three Gram-negative bacteria, two Gram-positive bacteria, and two fungi via disk diffusion method was investigated by Parsaeimehr et al. (2010). The results showed that all three species of *Ephedra* exhibited antibacterial and antifungal activity, and the highest antibacterial activity was related to *E. strobiliacea* and against *P. aeruginosa*. Dehkordi et al. (2015) determined minimum bactericidal concentration (MBC) and MIC of ethanolic extract of *E. procera* collected from a natural habitat in South-western of Iran on five bacteria, including *P. aeruginosa*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Bacillus cereus*, and *S. aureus*. The results demonstrated that the different bacterial species indicated diverse levels of sensitivity to the extract. The MICs of the *E. procera* extract were within concentration ranges of 250–500 μg/ml (*P. vulgaris*, *E. aerogenes*, and *B. cereus* = 250 μg/ml and *P. aeruginosa* and *S. aureus* = 500 μg/ml), and the respective MBCs were 500 μg/ml and > 500 μg/ml (*P. vulgaris*, *E. aerogenes*, and *B. cereus* = 500 μg/ml and *P. aeruginosa* and *S. aureus* > 500 μg/ml).

Other studies evaluated the extracts of *E. gerardiana* with several chemicals for antimicrobial potential against fungal and bacterial strains (Khan et al. 2017). The aqueous fraction showed no activities. In contrast, crude extract and the ethyl acetate fractions revealed promising antibacterial activities against *P. aeruginosa*, *K. pneumoniae*, and *B. subtilis*. However, all crude extracts and fractions were inactive on the fungal strains of *Aspergillus flavus* and *Aspergillus niger*, as compared to control (Khan et al. 2017).

The antibacterial activity of *E. sarcocarpa* was measured against bacteria *P. aeruginosa* (PTCC 1310), *Salmonella typhi* (PTCC 1609), *Bacillus pumilus* (PTCC 1319), *L. monocytogenes* (PTCC 1298), *E. coli* (PTCC 1533), and *Kocuria varians* (PTCC 1484), and fungal strains of *Candida glabrata* (PTCC 5297), *A. flavus* (PTCC 5006), and *A. niger* (PTCC 5154) (Rustaiyan et al. 2011). The results exhibited a significant decrease in bacterial growth in a zone of inhibition surrounding the disk using the disk diffusion method. Among examined bacterial strains, *P. aeroginosa* (MIC 16 μg/ml), *S. typhi* (MIC 64 μg/ml), *E. coli* (MIC 64 μg/ml), and *L. monocytogenes* (MIC 256 μg/ml) were more sensitive to crude extract. It was also showed mildly significant activity against *A. niger* (MIC 512 μg/ml), *A. flavus* (MIC 512 μg/ml), and *Candida glabrata* (MIC 512 μg/ml) (Rustaiyan et al. 2011).

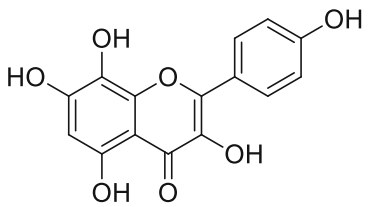
Anticancer Potential and Antioxidant Activity

Flavonoids and other phenolic compounds play an essential role in cancer prevention (Kopustinskiene et al. 2020), due to their antioxidant activity and potential to eradicate free radicals (Devi et al. 2021). Al-Awaida et al. (2018) investigated the cytotoxic effects of *E. aphylla* on the Vero cell line and breast cancer cell lines including T47D (derived from the pleural effusion cells) and MCF-7 (an epithelial cell line). This study also demonstrated that extracts of this plant with different solvents, including methanol, aqueous, chloroform, ethyl acetate, and hexane had a scavenging activity for H_2O_2 and NO. Furthermore, all extracts showed powerful antiproliferative potential for MCF7 and T47D tested cell lines and feeble cytotoxic activity against Vero normal cell line. From the anti-cancer potential effect of 72 species of medicinal plants reported in the West Bank Palestine, *E. alata* showed important effects on three different types of cancer (brain, liver, and colon), and *E. alata* had the highest impact on liver cancer (Jaradat et al. 2016). Ben-Arye et al. (2016) explored a herbal "wonder cure" for cancer. They demonstrated that *E. foeminea* Forssk. reduced cytotoxic effect of chemotherapy agents (carboplatin and cisplatin) on breast cancer cell cultures (MDA-MB231 and SKBR3).

The antioxidant and antiproliferative effects for the MeOH-soluble EtOH extract of *E. chilensis* reported that it had the highest antiproliferative effect for the MCF-7 (IC_{50} 1.29 ± 0.13 μg/ml) and PC-3 (prostate cancer cell line: IC_{50} 5.02 ± 2.45 μg/ml) cancer lines (Mellado et al. 2019). *E. campylopoda* is another species that could be a promising resource of natural products with antioxidant, anti-inflammatory, and antiproliferative capacities. This study performed on *E. campylopoda* suspended in 3 diverse solvent systems, containing distilled water, methanol, and ethanol, showed that the alcoholic extracts were better than the aqueous one in terms of their chemical combination (Kallassy et al. 2017). In a study to prove the usages of *E. intermedia* in Pakistani folk medicines, the antioxidant activity, screening of the phytogenic chemical combinations, and determination of its alkaloids were evaluated. The results indicated that the methanolic

extract of this plant has antioxidant activity and powerful activity in inhibiting oxygen free radicals, and the half-maximum inhibitory concentration (IC_{50}) is equal to 5 μg/ml, which is close to the reference standard ascorbic acid (IC_{50} 3 μg/ml) (Gul et al. 2017).

Multiple cellular processes such as cell proliferation, scattering, cell motility, and angiogenesis are regulated by hepatocyte growth factor and its receptor c-Met (Sierra and Tsao 2011). Many studies have reported that c-Met is overexpressed in various types of carcinomas, including renal, hepatocellular, lung, colon, and breast carcinomas. Hyuga et al. (2013) described that the flavanol herbacetin (**15**), isolated from the non-alkaloidal constituents of *Ephedra* herb extract (EHE), exhibited antimetastatic effects by the suppression of motility of breast cancer cells (MDA-MB-231) due to its inhibitory activity towards the c-Met receptor. These findings suggest that some of the pharmacological actions of *Ephedra* decoction may occur due to its non-alkaloid components, thus avoiding the adverse effects of ephedrine alkaloids (Hyuga et al. 2013). In recent years, some *Ephedra* species have gained interest as an alternative to cancer treatment, an example of this is *E. foeminea*, which has been widely used to treat this condition.



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Anti-diabetes

Diabetes mellitus, disorder of carbohydrate metabolism, is one of the major causes of morbidity and mortality among common disorders worldwide (Dal Canto et al. 2019). This disease is characterized by high levels of blood glucose, which is caused by a relative or absolute deficiency of insulin secretion, resistance to the function of this hormone, or both of them simultaneously (Defronzo and Abdul-Ghani 2011). Consequences are related to the diseases that develop as a result of chronic diabetes mellitus. These include diseases of large blood vessels (macrovascular disease, including coronary heart disease and peripheral arterial disease) and small blood vessels (microvascular disease, including retinal and renal vascular disease), as well as diseases of the nerves.

It was reported that inhibition of α-amylase and α-glucosidase enzymes has an important implication in the treatment of type 2 diabetes mellitus. Hydrolyzing enzymes such as intestinal α-glucosidase and pancreatic α-amylase play essential roles in hydrolysis and carbohydrate uptake (Li et al. 2017). Therefore, this is an effective way to manage blood sugar levels by inhibiting the activity of these enzymes (Striegel et al. 2015). When their function is inhibited, the breakdown of complex sugars such as starch can be delayed, thereby prolonging digestion time and consequently preventing an excessive postprandial rise in blood glucose level. Ben Lamin et al. (2019) reported that the decoction of *E. alata* at a concentration of 300 mg/kg of body weight inhibited the activity of α-amylase and α-glucosidase enzymes, which has a more significant effect on α-glucosidase, and it is of great pharmaceutical importance.

A suitable mechanism for treating or preventing type 2 diabetes mellitus could consist of inhibiting dipeptidyl peptidase IV (DPP-IV) and thus raising the half-lives of incretin hormones (Opinto et al. 2013). DPP-IV is a ubiquitous aminopeptidase that selectively picks up *N*-terminal dipeptides from peptides by alanine or proline in the second position (Ojeda et al. 2014; Costante et al. 2015). The investigation of Ojeda-Montes et al. (2017) showed that *Ephedra* alkaloids, such as ephedrine (**1**), could be considered new inhibitors of DPP-IV (Ojeda-Montes et al. 2017). Preethi in a review study of herbal medicine for treating diabetes mellitus reported 802 plant species including *E. distachya* and *E. alata* aerial stems which are effective in treating diabetes (Preethi 2013).

Lee et al. (2014) showed inhibitory effects of quinaldic acid (**14**) from *E. pachyclada* Boiss. on α-glucosidase and α-amylase. The antidiabetic activity was associated to the presence of the carboxyl group in the isolated active compound, as an inhibitor of the α-glucosidase and α-amylase activities, and suggested that the quinoline-2-carboxylic acid derivatives can be appropriate alternatives for the synthesis of antidiabetic agents.

Shojaei et al. (2017) evaluated the antidiabetic activity of *Ephedra* in streptozotocin-induced diabetic rats. This experimental study was carried out on 40 male Wistar rats. It was randomly divided into four groups: A, B, C, and D (A, the healthy group: and B, C, and D, streptozotocin-induced diabetic groups). Diabetes mellitus was induced in rats of groups B and D with single intraperitoneal injection of streptozotocin. Statistically, a significant difference was shown among the diabetic and healthy groups. The mean blood glucose level raised remarkably in groups B and D on the 3rd day in comparison with other groups. Therefore, *Ephedra* extracts have potential as a phytotherapeutic agent to control diabetes.

Anti-rheumatoid Arthritis Activity

Rheumatoid arthritis (RA) is an immune-mediated disease characterized by prolonged inflammation in some joints. The signs and symptoms of RA are incessant joint synovial inflammation due to the influence of actuated T lymphocytes and macrophages, pannus growth, and consequent destruction

of adjacent bone and cartilage tissue (Lin et al. 2013). This disease can rapidly develop into multisystem inflammation with changeless joint damage, then causing premature mortality and disability (Zheng et al. 2014, Guo et al. 2018). T and B lymphocytes, macrophages, fibroblasts, and pro-inflammatory cytokines, mainly interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF-α), along with lipoxygenases (LOX) and cyclooxygenases (COX) play significant roles in rheumatoid arthritis pathogenesis, affecting articular cartilage hyperplasia (Sukketsiri et al. 2016; Singh et al. 2020; Makuch et al. 2021). In addition to pro-inflammatory cytokines, increased oxidative stress has been distinguished as one of the essential predisposing factors of joint destruction in rheumatoid arthritis. Augmented cytokine production stimulates inflammatory cells, for example, macrophages and neutrophils to evacuate ROS (reactive oxygen species) in synovial fluid, which mediates tissue injury (Ponist et al. 2019).

The effects of aqueous and ethanolic extracts of *E. gerardiana* on arthritis in Sprague Dawley rats (are an outbred multipurpose breed of albino rat used extensively in medical and nutritional research) were investigated by Uttra et al. (2018). They showed that the extract of *E. gerardiana* could downregulate prostaglandin E2 (PGE2), COX2, IL-1β, IL-6, TNF-α, and nuclear factor-κB (NF-kB), and upregulate IL-10 and IL-4. Hence, these results showed that *Ephedra* extracts considerably attenuated arthritis in rats by reducing the levels of pro-inflammatory and enhancing the levels of anti-inflammatory mediators that might be used as a therapeutic agent for treating human arthritis. The anti-arthritis effects of *E. gerardiana* have also been extensively investigated by *in vivo* and *in vitro* models. The anti-arthritic potential of the ethanol extract and its *n*-butanol, ethyl acetate, and aqueous soluble fractions was tested. *In vitro* assays involved egg albumin denaturation and thermally induced bovine serum albumin denaturation. In addition, membrane-stabilizing assay was performed in a concentration range of 50–6400 μg/ml for the tested extracts and fractions, while *in vivo* study included formaldehyde-induced arthritis at 50, 100, and 200 mg/kg doses. The fractions and crude extract prevented protein denaturation and stabilized red blood cell membrane in the concentration-dependent manner, with maximum efficacy achieved at concentration of 6400 μg/ml ($p < 0.001$). In the formaldehyde method, the extract and fractions dose-dependently decreased injected paw diameter and volume, with the maximal decrease in 200 mg/kg ($p < 0.001$) (Uttra 2017).

Wang et al. (2016) examined ESP-B4 (an acidic heteropolysaccharide from the stems of *E. sinica*) for treating arthritis. In this study, the attributes of ESP-B4 on lipopolysaccharide (LPS)-induced THP-1 (is a human monocytic cell line derived from an acute monocytic leukemia patient) promonocytic cells and adjuvant-induced arthritis in Wistar rats by toll-like receptor 4 (TLR4) were evaluated. The results demonstrated that ESP-B4 prevented the release of LPS-induced, NF-kB mediated, inflammatory cytokines by a TLR4-associated process and improved systemic inflammation in arthritis rats (Wang et al. 2016).

The anti-arthritic and anti-inflammatory effects of aqueous extract of *E. sinica*, at herb-acupuncture, on the inflammatory responses of arthritis were examined by phorbol 12-myristate 13-acetate/LPS-induced human macrophage and adjuvant-induced arthritic rat (Yeom et al. 2006). For the evaluation of the *E. sinica* herb as a new anti-arthritic treatment in acupuncture, a polyarthritic rat model was created with heat-killed *Mycobacterium tuberculosis*, and 50 μl of aqueous extract of *E. sinica* was subcutaneously injected to the ST36 acupoint (in acupuncture is located four finger widths down from the bottom of your kneecap) in each knee joint. The mRNA expressions of IL-6 and TNF-α genes showed closely induced in the arthritic rat joints were changed to the normal levels by the *E. sinica* therapy. In the case of IL-1β, the improvement was not significant but substantial (Yeom et al. 2006).

Hypertension

Hypertension is the main modifiable risk factor for cardiovascular disease (El-Gazzar et al. 2017; El-Shebiny et al. 2019; Fuchs and Whelton 2020). Resistant hypertension is described as blood pressure that remains above the goal despite the simultaneous usage of three antihypertensive agents of diverse classes taken at maximum tolerated doses (Calhoun et al. 2008). Preferably, one of the three agents should be diuretic, and all medications administered at an optimal dose (Calhoun et al. 2008). According to this definition, resistant hypertension includes patients whose blood pressure is controlled by more than three drugs (Calhoun et al. 2008).

Ephedra alkaloids have a remarkable potential to raise blood pressure (Haller and Benowitz 2000; Vora and Mansoor 2005). Ephedra's combination with caffeine as a dietary supplement increases blood pressure explicitly. In a controlled clinical trial, an increase in systolic blood pressure of 124 ± 12 mm Hg related to 119 ± 10 mm Hg (*p*-values=0.009) was observed in users of supplements containing *Ephedra* alkaloids compared with placebo subjects (McBride et al. 2004; Sander 2011). Richard and Jurgens (2005) reported that *E. sinica* increased blood pressure, and patients with hypertension should not use it.

Anti-Alzheimer Activity

Alzheimer's disease (AD), the most common form of dementia between the elderly, is known by advanced cognitive dysfunction, and it mostly presents with memory loss and depression. One of the pathologic signs of AD is senile plaques that are extracellular accumulation of insoluble β-amyloid (AB)

protein (Long and Holtzman 2019). The AB peptide is a product of the proteolytic cleavage of APP (amyloid precursor protein) by β- and γ-secretases. Since AB deposits in senile plaques have been admitted as one of the leading causes of Alzheimer's disease pathology, modulation of AB toxicity has considered being an essential therapeutic approach to control the beginning of Alzheimer's disease (Park et al. 2009). Park et al. (2009) examined the neuroprotective effects of traditional oriental herbal medicines against β-amyloid-induced toxicity, and reported that among 400 methanolic extracts of medicinal plants, the extract of herbs such as *E. sinica* could protect PC12 cells (a cell line derived from a pheochromocytoma of the rat adrenal medulla) against isquemic insult, which significantly increases the beta amyloid (Aβ) production with an effective dose (ED_{50} < 100 μg/ml) (Fig. 2).

Inhibition of Chemokines

Chemokines (or chemotactic cytokines) are a structurally linked collection of small proteins that, in coordination, recruit different leukocytes and stimulate their migration to corresponding target site receptors (Bhusal et al. 2020). There are at least 18 signal-transducing receptors and 44 chemokines in humans (Zlotnik and Yoshie 2012). Chemokines play leading roles in different biological processes such as homeostatic migration and inflammatory mobilization of leukocytes, the homing of lymphocytes, cell migration, and tumor-homing of cancer cells during development, cancer metastasis, and angiogenesis (Fujita et al. 2015). Chemokine receptors are owned by the seven-membrane G protein–coupled receptor (GPCR) family (Yang et al. 2021). Since there are some of the drugs targeting GPCRs that have successfully developed thus far, chemokine-chemokine receptor (CCR) axes are considered to be promising drug targets for inflammatory and immunological diseases (Subramaniam et al. 2012; Martin-Blondel et al. 2016). Chemokine receptors CCR4 and CCR3 are preferentially expressed via mast cells, TH2 (T helper type 2) cells, and or eosinophils, all of them involved in the pathogenesis of allergic diseases.

Matsuo et al. (2016) reported *Ephedra* herb as a specific antagonist of TH2-specific chemokine receptor types CCR3, CCR4, and CCR8. Yiping et al. (2017) investigated the effects of serum including *E. Sinica* on the migration of interstitial macrophages (IMs) and alveolar macrophages (AMs) in normal rats. Rats in this study were randomly divided into *E. Sinica* and blank serum groups. After treatment, serum was extracted from the rats. IMs and AMs were separated from normal rats and cultured. Furthermore, the effects of herb-medicated serum on normal rat AM and IM chemotactic migration were determined with transwell assays, and the CC chemokine receptor CCR5 and CCR2 protein levels were examined with western blotting. CCR2 and CCR5 proteins were expressed in the AM cell surface and showed remarkably higher expression in *E. sinica*–medicated serum group (Yiping et al. 2017).

The evaluation of the bisflavonoids ephedrannin A (**16**) and B (**17**), two hypotensive principles of roots of *E. sinica*, showed that the both prevent lipopolysaccharide-induced inflammatory mediators by suppressing NF-κB activation in RAW 264.7 macrophages (a macrophage-like, Abelson leukemia virus transformed cell line isolated from BALB/c mice). These compounds used their anti-inflammatory

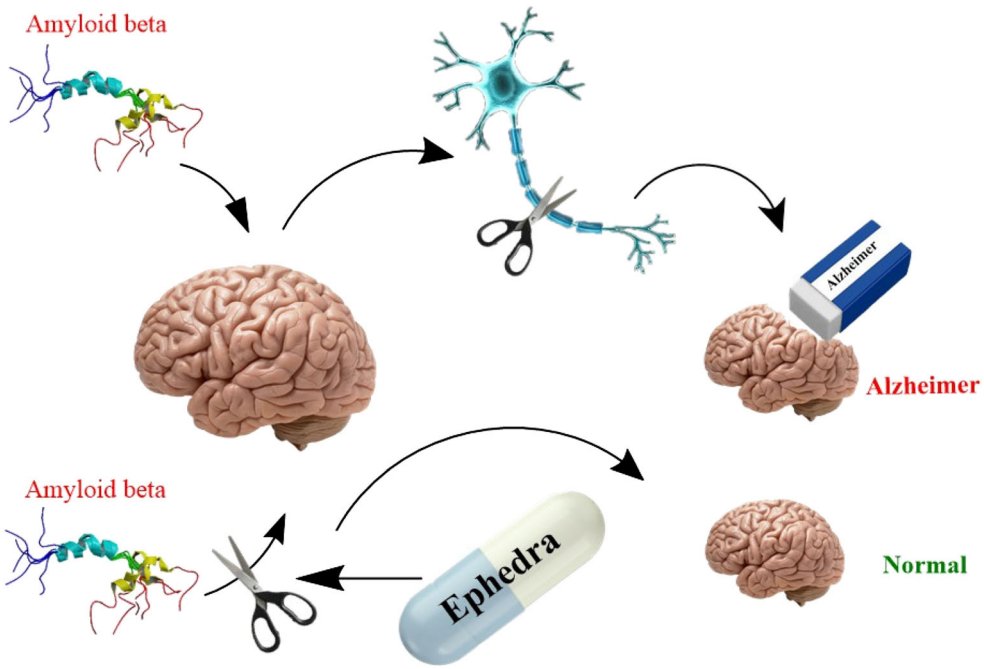
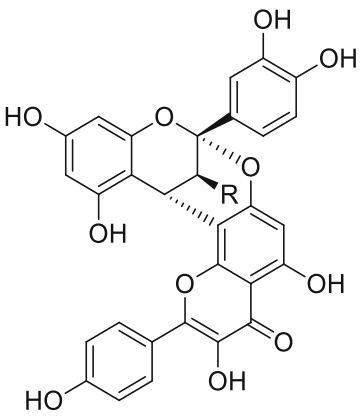


Fig. 2 The schematic image of the effect of *Ephedra* on Alzheimer's disease

functions on LPS-stimulated macrophages with suppressing the translocation of NF-κB and the phosphorylation of p38 mitogen-activated protein (MAP) kinase (Kim et al. 2010).



16 R=OH
17 R=H

Lim et al. (2016) investigated the inhibitory effects against inflammation responses of Ma Huang Tang (Ma Huang means "ephedra," and Tang means "decoction"), which is a Chinese traditional herbal medicine comprising six medicinal herbs where the major herbal ingredient is *E. sinica*. It was initially described in Shanghan Lun (Treatise on Cold Damage Diseases) at the end of the Han Dynasty (189 AD–220 AD). Ma Huang Tang is often used to promote sweating, relieve asthma, and treat fever with anhidrosis, body coldness, headache, body pain, thin and white tongue coating, and tight pulse caused by wind-cold, influenza, acute bronchitis, bronchial asthma, upper respiratory tract infection, and acute febrile disease. In Japan, Kampo medicine is widely used to treat upper respiratory tract infections and influenza (He et al. 2012). *Ephedra* decoction was tested in the skin with HaCaT (a spontaneously transformed aneuploid immortal keratinocyte cell line from adult human skin) keratinocytes. The decoction repressed production of macrophage-derived chemokine (MDC/CCL22), and activation-regulated chemokine (TARC/CCL17), interleukin-8 in tumor necrosis factor-α, and interferon-γ stimulated HaCaT cells (RANTES/CCL5). Furthermore, Ma Huang Tang repressed TNF-α and IFN-γ-stimulated STAT1 phosphorylation into a dose-dependent manner and nuclear translocation in human keratinocyte cells (Lim et al. 2016).

Anti-neuro-inflammatory

Inflammatory responses were triggered by several immune and inflammatory cells, such as T cells, macrophages, neutrophils, and microglia (Shabab et al. 2017). Neuro-inflammation is a defensive mechanism to improve damaged neuronal and glial cells in the CNS. Neuroinflammation mediated with microglia, the inhabitant brain macrophage, astrocytes, neutrophils, T cells, neurons, mast cells, and inflammatory mediators released from these cells (Shabab et al. 2017). After the diagnosis of the disorder in homeostasis, microglia activate the production of cytokines, such as TNF-α, IL-1β, IL-6, and inflammatory mediators, containing ROS, nitric oxide (NO), PGE2, inducible nitric oxide synthase (iNOS), and COX-2 (Gaire et al. 2015; Stamouli and Politis 2016). Neuroinflammation is at first a protective response in the brain, but additional inflammatory responses are harmful, and it prevents neuronal regeneration (Kempuraj et al. 2016; Russo and Mcgavern 2016).

In the study conducted by Park et al. (2019), gold nanoparticles (Au NPs) synthesized by the extract of *E. sinica* were investigated for their anti-neuroinflammatory effects on LPS-stimulated microglia associated to the production of pro-inflammatory mediators like prostaglandin E2, reactive oxygen species, and nitric oxide and cytokines like TNF-α, IL-6, and IL-1β in lipopolysaccharide via enzyme-linked immunosorbent assay (ELISA) and flow cytometry. It was found that gold nanoparticles containing *E. sinica* extract significantly reduced LPS-induced production of proinflammatory mediators and cytokines that was relevant to repressed transcription and translation of inducible nitric oxide synthase and cyclooxygenase-2 (Park et al. 2019).

Anti-hyperlipidemia

Hyperlipidemia is described as an abnormal metabolism of lipid or high levels of fat in the blood, such as triacylglycerides (TGs), total cholesterol (TC), free fatty acids, low-density lipoprotein, and very-low-density lipoprotein (Fan et al. 2015). Hyperlipidemia can cause complications such as changes in blood density, and blood flow that may cause arteriosclerosis, as well as pathologic changes in the tunica intima, and microcirculation disorder. Hyperlipidemia has been reported to be related to cardiovascular disease and diabetes. Accordingly, reducing the levels of blood lipids has high importance for the inhibition and treatment of atherosclerosis and diabetes (Ziegler et al. 2019).

Fan et al. (2015) reported the hypolipidemic potential of *E. sinica* extract in dietary hyperlipidemic mice. In this study, a high-fat diet was used to induce hyperlipidemia in mice, and a total of 48 mice randomly divided into six groups (normal control = G1, model control = G2, positive control = G3, ephedrine alkaloids = G4, ephedra polysaccharide = G5, and ephedra non-alkaloids = G6). Mice in the ephedra polysaccharide, ephedrine alkaloid, and non-alkaloid groups were orally administered by 1.26 mg/g respective extractions, for 4 weeks, and their weights were recorded weekly. In the serum were noted TGs, TC, high-density lipoprotein cholesterol, malondialdehyde (MDA), and the activity levels of

superoxide dismutase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). The liver factor; the weight, serum levels of TG, TC, and MDA; and activities of AST and ALT were remarkably lower ($p < 0.05$) in the mice treated with non-alkaloid *E. sinica*.

Lee et al. (2019) investigated molecular targets and the effects of methanol extract of *E. sinica* and *E. intermedia* on a high-fat diet–induced hyperlipidemic Institute of Cancer Research mice (ICR mouse is a strain of albino mice, widely utilized as testing animals in different biomedical research fields). *Ephedra* extract was orally administered with 100 mg/kg body weight/day for 3 weeks. *Ephedra* extract administration significantly reduced triacylglyceride and TC levels without change in the body weight of the studied mice (Lee et al. 2019). In addition, gene expression levels at the livers of *Ephedra*-treated mice were reformed at 48.4 and 34% of those down- or upregulated by hyperlipidemia, respectively. The study showed the preventive effects of *Ephedra* on hyperlipidemia in mice, possibly by the regulation of DNA repair and the expression of energy metabolism-related proteins and genes (Lee et al. 2019).

Anti-asthma

Asthma is a chronic airway inflammation, like chronic rhinitis, chronic otitis media, chronic pharyngitis, chronic sinusitis, and chronic laryngitis, which embraces a wide array of potential causes and conditions. This illness is a disorder of the airways caused by a large number of cells, including T lymphocytes, macrophages, neutrophils, eosinophils, mast cells, and epithelial cells (Mims 2015).

Generic medications in asthma treatment include bronchodilators and anti-inflammatory drugs. One of the essential bronchodilator drugs used to relieve bronchoconstriction in obstructive pulmonary disease, and mostly asthma, is β_2-adrenoceptor stimulation drugs (Hsu and Bajaj 2021). Shakeri et al. (2019) investigated the effects of medicinal herbs on β2-adrenoceptors of tracheal smooth muscle. They found in *E. sinica* a relaxant effect on tracheal smooth muscle with a stimulatory effect on the β_2-adrenoceptor mechanism.

Ephedra improves bronchial asthma symptoms through the TLR9 pathway. Jiao et al. (2018) investigated the possible mechanisms of *Ephedra* on ovalbumin (OVA)-induced acute bronchial asthma in mice. In this study, an asthma-associated protein-protein interaction network was created. Then, the acute bronchial asthma mice models were created with exposure to aerosolized 1% ovalbumin for 30 min in day for 1 week, and the mice were administered with 2, 4, or 8 g/kg of *Ephedra* daily. To assess the therapeutic effect, abdominal breathing time, sensitization time, eosinophils in bronchoalveolar lavage fluid, and trachea and tissue pathology were investigated, and associated genes were measured. Also, the expression level of TLR9 in trachea and lung tissues was determined with immunohistochemical staining. The results showed that ephedra had an LD_{50} (lethal dose 50%) of 19.2 g/kg for asthma, while at high doses (8 g/kg) effectively increased the sensitization time and abdominal breathing time and reduced mitigated pathological changes, and OVA-induced eosinophilic airway inflammation. Furthermore, the result of RNA sequencing assay showed that the high dose of *Ephedra* led to significant reduction in the levels of TLR9, TRAF6 (tumor necrosis factor receptor associated factor 6), TAB2 (TGF-beta activated kinase 1 (MAP3K7) binding protein 2) in the lung tissue, and immunohistochemical assay which demonstrated the downregulation of TLR9. Also, molecular docking showed that six *Ephedra* compounds (echinatin, isoliquiritigenin, isoliquiritigenin, neoisoliquiritin, neochlorogenic acid, and 8-*O*,4′-diferulic acid, all belongs to non-alkaloid structure) potentially mediated the TLR9 signaling pathway.

Munns and Aldrich (1927) examined twenty-two children with bronchial asthma by oral administration of ephedrine sulfate. The results of this study showed, in twelve children, relief was afforded to patients who were in the paroxysmal stage or had a severe persistent cough, usually from 30 to 45 min after the first dose. Nine of the patients had a persistent cough as the main sign, which was relieved effectively in eight instances.

Another study showed that combination of *Ephedra* extracts and gypsum (calcium sulfate dihydrate, $CaSO_4 \cdot 2H_2O$) has anti-asthmatic properties (Mei et al. 2016). The antiasthmatic activity of *Ephedra*-gypsum was examined by an OVA-induced asthmatic rat model. In this study, 36 male rats were randomly distributed into 6 groups and were alternately sensitized and challenged with exposure to mists of ovalbumin (Mei et al. 2016). Dexamethasone or extracts in the amounts of 6, 12, and 24 g/kg were administered 45 min before the allergen challenge for 8 days. Finally, the latent period and the weight of the wet to dry ratio of the lung were determined. Furthermore, the eosinophils and white blood cell (WBC) count were measured via a YZ-Hemavet Analyzer. The tests showed that the *Ephedra*-gypsum mixture lengthened the latent period, declined OVA-induced increases in WBC and eosinophils, and reduced dry weight ratio and the wet of the lungs at the anti-asthmatic test (Mei et al. 2016).

Acute Liver Failure

Fulminant hepatic failure or acute liver failure (ALF) is a syndrome distinguished with a sudden onset, icterus, and hepatic encephalopathy in the lack of pre-existing liver disease (Anand et al. 2020; Paugam-Burtz et al. 2020). In this disease, the liver biopsy reveals usually diverse degrees of inflammation and extensive hepatic necrosis (Lefkowitch 2016). ALF displays very high mortality caused by alcohol, viral infection, or drugs (Butler et al. 2018). This disease is a complex multi-

organ system process that leads to renal and respiratory failure, cerebral edema, coagulopathy, hemodynamic disorder, and sepsis (Newland 2016).

D-Galactosamine and LPS-induced hepatic injury are an experiential model of fulminant hepatic failure where TNF-α plays a pivotal role. Yamada et al. (2008) evaluated the effect of *E. sinica* extract on this mice model. They observed that the lethality of mice treated with *E. sinica* and D-galactosamine and lipopolysaccharides was remarkably reduced compared with that of mice untreated via *E. sinica*. The hepatic cell apoptosis and inflammatory cell infiltration were low in mice treated with *E. sinica*. Also, serum total bilirubin and alanine aminotransferase activity, TNF-α levels, and caspase 3, 8, and 9 activities in the liver were significantly lower in mice treated with *E. sinica*.

Ghasemi et al. (2014) examined protective effects of *E. pachyclada* extract on mouse models of carbon tetrachloride (CCl_4)–induced acute and chronic liver failure. In this study, to create models of chronic and acute liver injuries, male SW1 (a model which responds poorly to several forms of immunotherapy) mice were intraperitoneally injected by 1 ml/kg body weight of CCl_4 biweekly for 42 days and a single dose of 2 ml/kg body weight, respectively. In the test groups, mice models were treated by low (140 mg/kg body weight) and high (1400 mg/kg body weight) doses of the *E. pachyclada* extract. Water- and olive oil (1:1(v/v))–treated mice were considered controls, respectively. The results showed the antioxidant potential of *E. pachyclada* extract in the mice model and a significant decrease of all parameters of CCl_4-induced acute and chronic liver injury, such as the relative liver weight, fibrosis, inflammation, necrosis, and serum ALT and aspartate transaminase.

Methods of Consumption

Extracts, dried herbs, tinctures, and alkaloids isolated from this herb are used. The total alkaloids (300 mg) of this plant can be consumed daily, in which it is better to take 15–30 mg as a single dose for adults and 2 mg per kg of bodyweight of the alkaloids of this plant. In addition, ephedrine is used in the form of 0.01 to 0.05 g tablets at home, which can be prevented by taking 0.05 g tablets 2 h before the onset of the asthma crisis, but in any case, it should be considered tolerated in the patient. Depending on the patient's tolerance, 0.5 g tablets can be used every 2 or 3 days on an empty stomach. Moreover, for external use, 0.10 g suppository or 3% ephedrine solution in the dose of 1 or 2 drops in alfalfa alum or 3 to 5% ointment are utilized to influence the nasal mucosa. By inhalation, a 1 to 3% solution of ephedrine prepared in equal proportions with glycerin and water is used (Ghavam and Soleimaninejad 2020).

Pharmacokinetics

In traditional dosage form of ephedrine, several pharmacokinetics have been reported (Pickup et al. 1976; Kanfer et al. 1993; Vanakoski et al. 1993). The reported mean pharmacokinetic parameters for 22 mg Ephedrin (in Ephedrin solution) were as follows: Ka = 2.35 h^{-1}, T_{lag} = 0.18 h, AUC = 814 ng·h/ml, $t_{1/2}$ = 6.75 h, V_{ss}/F = 215.6 l, Cl/F = 23.3 l/h, t_{max} = 1.81 h, C_{max} = 79.4 ng/ml (White et al. 1997).

Toxicology

Generally, the use of ephedrine in sports competitions is illegal, and overuse is addictive. It is recommended to take this substance with the permission of a physician because many studies and experiments have shown that it causes inconsistencies. Laboratory research has shown that taking ephedrine causes uterine contractions, so pregnant women should not take it. Another side effect of *Ephedra* is sleep disturbance, so people with insomnia should avoid it. Some other side effects of this herb include drying the mouth; complications due to increased energy levels in the body such as anxiety, hot flashes, sleep disorders, increased sweating, and insomnia; neurological disorders such as insanity, burning, itching, tremors, fatigue, and headache; disorders in the circulatory system, such as the possibility of stroke; and high blood pressure and complications such as allergies, increased urination, and diarrhea (Ghavam and Soleimaninejad 2020).

Perspectives and Future Directions

The results of this review showed that *Ephedra* has high potential in the treatment of several diseases such as diabetes, Alzheimer's, asthma, hyperlipidemia, hypotension, and rheumatism. This plant has antimicrobial, anticancer, and antioxidant effects and is also used as a supplement. Although this plant has various medicinal and therapeutic properties, due to its side effects, more complete clinical studies and tests should be performed on it, and the effect of this plant on other diseases and clinical applications can also be investigated.

Conclusion

Ephedra species are a source of bioactive natural products that attract researchers' attention since they can exhibit complementary biological and therapeutic effects against diseases. Also, the investigations about chemical composition and pharmacological influences of *Ephedra* herb are rising annually, which can provide new insight into this herb composition and its clinical applications. This herb contains many therapeutic and therapeutic effects, can be used as supplements, and

influences the central nervous system (CNS), blood pressure, Alzheimer's disease, asthma, rheumatoid arthritis, allergic diseases, antimicrobial, anticancer and antioxidant, anti-diabetes, anti-neuroinflammatory, and anti-hyperlipidemia properties. In the future, *Ephedra* herbs will continue to play a notable role in the pharmaceutical industry and public and primary health care.

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