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•Review•

A review of the phytochemistry and pharmacological activities of *Ephedra* herb

MIAO Shuang-Man[1, 2Δ], ZHANG Qi[1, 2Δ], BI Xiao-Bao[3], CUI Jin-Long[1*], WANG Meng-Liang[1]

[1] *Institute of Applied Chemistry, Shanxi University, Taiyuan 030006, China;*
[2] *Modern Research Center for Traditional Chinese Medicine, Shanxi University, Taiyuan 030006, China;*
[3] *Centre for Biomimetic Sensor Science (CBSS), School of Materials Science & Engineering, Nanyang Technological University, Singapore 637553, Singapore*

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[ABSTRACT] *Ephedra* herb is a traditional Chinese medicine with a long history. Conventionally, it was used as a folk phytomedicine in many ancient medical books and traditional prescriptions. Up to date, a variety of specific ingredients have been found in *Ephedra* herb, mainly including alkaloids, flavonoids, tannins, polysaccharides, organic acids, volatile oils, and many other active compounds. These components from *Ephedra* herb account for its use as the accurate treatment of cold, cough, cardiovascular and immune system disease, cancer, microbial infection, and other diseases. Moreover, with the fast development of novel chemistry and medicine technology, new chemical constituents and pharmacological effects of *Ephedra* herb are increasingly identified, demonstrating their great potential for various diseases treatment. Therefore, further detailed understanding and investigation of this ancient herb will offer new opportunities to develop novel therapeutics. This study systematically reviews its progress of phytochemistry, traditional and modern pharmacology based on research data that have been reported, aiming at providing useful insight for commercial exploitation, further study and precision medication of *Ephedra* herb in future.

[KEY WORDS] Traditional Chinese medicine; Phytochemistry; Ethnopharmacology; Bioactivity; Phytomedicine

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Introduction

Ephedra herb is a traditional Chinese medicine that has been used for over 5000 years. It was originally recorded at *Shen Nong Ben Cao Jing* and classified as middle-level products. According to ancient medical books, Mahuang and Mahuanggen from the stems and roots of *Ephedra* plants, respectively, are considered as two kinds of herbal medicines, and they have completely opposite pharmacological effects in regulating sweat secretion and blood pressure [1]. In China, more than 60 classical prescriptions comprising *Ephedra* herbs have been recorded in the *Chinese pharmacopoeia* (2015 edition). Numerous folk prescriptions have been used to treat lung diseases, such as cough and asthma, and other common diseases, including inflammatory pain, bruises, rhinitis, and arthritis. Likewise, in ancient India and Japan, records have shown that *Ephedra* herbs are mainly used as medicines for cold and asthma [2].

Ephedra herb is a common phytomedicine with a long history and a wide range of pharmacological effects. Recently, many researchers have conducted in-depth studies on the pharmacological effects of extracts or monomeric compounds from *Ephedra* herb. It appears that not only the stems, roots, but chemical components of *Ephedra* fruits also have the multiple pharmacological functions. Additionally, there were approximately 10 kinds of pharmaceutical dosage forms of *Ephedra* herb statistically, including ordinary tablets, chewable tablets, capsules, syrups, drops and so on. And more than 500 kinds of drugs are consisted of *Ephedra* herb [3]. Many countries, such as the United States and China, are the leading ones in the research and development, production, and consumption of *Ephedra* herb. Thus, it is necessary to fully excavate the efficacy of *Ephedra* herbs. Additionally, a systematic report on its characteristics, chemical composition, and pharmacological effects will provide a solid foundation for the new development and application of *Ephedra* herb.

Botanical Characterization

Ephedra plants are gymnosperms with approximately 67

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[*Corresponding author] Tel: 86-13934636596, Fax: 86-351-7016101, E-mail: CJL717@163.com.
ΔThese authors contributed equally to this work.
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species worldwide and often distributed in arid and sandy soil regions of Asia, America, Southeastern Europe, and Northern Africa. Fifteen species and four varieties of *Ephedra* plants are found in China, and they grow optimally in saline alpine sandy soil with pH = 8 [4]. Most *Ephedra* species were used as traditional medicines in the folk, however, each edition of Chinese Pharmacopoeia only incorporates three *Ephedra* species as the original plants of traditional Chinese drug "Mahuang", namely, *E. sinica* Stapf., *E. intermedia* Schrenk, and *E. equisetina* Bunge. Among them, *E. sinica* is the most commonly used species. According to *the flora of China*, it is a perennial herbaceous shrub plant, which is approximately 30–70 cm tall (Fig. 1). Its yellowish-green herbaceous stem has many branches of nodes, and 3–4 cm long internodes can be found between small branches. Its leaves are scaly and reduced to membranous matrixes that can attach themselves on nodes. It is a dioecious plant that flowers are pedunculate, terminal, or lateral in May. The male cones are ovoid or elliptical in shape and have a compound spike; the female cones grow alone. Fleshy red bracts called *Ephedra* fruits containing two seeds emerge and they are ripe in July. The plant has creeping, tawny, and lignified rhizomes, which are distributed 10–60 cm vertically and 8–10 m^2 flatly underground, thereby forming a dense root network. As the plant ages, the horizontal rhizomes thicken and lengthen in its dense network to promote the supply of water and nutrients to the branches on the ground, accelerate the growth of plants, and enhance its ability to survive drought and resist cold. *Ephedra* herb is not only widely used as a traditional Chinese medicine to treat various diseases, but has the ability to maintain sand and soil in arid desert areas, and conserve water [5].

Development of Medicinal Value of *Ephedra* Herb

Ephedra herb has undergone traditional efficacy and modern pharmacological research. Traditionally, it is mainly used as a whole plant or in combination. Modern use is mainly carried out using crude extracts or monomers of plant samples. Here we summarize the medicinal value of Mahuang and Mahuanggen, and crude extracts or monomers of *Ephedra* herbs, aiming to provide detailed evidence and theoretical basis for the better understanding of *Ephedra* herb and promoting the precise use of *Ephedra* herb.

Progress in Traditional Pharmacology

According to ancient Chinese herbal literature, Mahuang and Mahuanggen are traditional Chinese medicines from the stems and roots of *Ephedra* plants, respectively. In these two medicinal parts, Mahuang is pungent and slightly bitter and has a warm nature, and it belongs to lung and bladder meridians for sweating and dispelling cold, relieving asthma and cough, inducing diuresis, and alleviating edema, and it is used to treat cold, typhia, and lung diseases [6]. Besides using alone, Mahuang can also be combined with other Chinese herbs to treat various diseases. For example, Mahuang–Shigao, Mahuang–Changpu, Mahuang–Jiegeng and Mahuang–Qianhu were used to treat infantile enuresis, alopecia,

Fig. 1 Plant habitat (A), growing state (B) and morphological structure (C) of *Ephedra sinica* in north of Shanxi province, China. *E. sinica* always can be found in desert, barren and saline-alkali soil. It has no leaves and belongs to gymnosperm, and its aerial and underground parts are the origins of Mahuang and Mahuanggen as traditional Chinese medicines, respectively

diarrhea and infantile dysentery, seperately [7]. In addition, as the commonly used couplet medicines, Mahuang–Gancao (22.4 $g\cdot kg^{-1}$) not only can exert significant diuretic effects [8], but has an anti-inflammatory effect. There have been many investigations showing the anti-inflammatory effect of Mahuang–Gancao. For example, it can significantly inhibit pleural effusion induced by carrageenan and reduce the amount of leukocytes in the inflammatory area to exert a significant anti-inflammatory effect [9]; it can be used to treat acute inflammation by inhibiting the release of inflammatory mediators and preventing the increase in capillary permeability; the research conducted by Zhao *et al*. [8] also disclosed the mechanism to treat chronic inflammation by which the formation of cotton ball granuloma is blocked through inhibiting cell proliferation.

Besides, the scope of treatment of Mahuang was further expanded recently. For example, Mahuang–Wutou–Xixin and Mahuang–Lianqiao–Chixiaodou decoction is mainly used to treat respiratory diseases and hepatitis virus, respectively [10, 11]. Mahuang–Lianqiao–Chixiaodou decoction also can reduce transforming growth factor-β1 concentration in serum and urine, eliminate renal fibrosis, and protect kidney function [12]. More importantly, some skin diseases were treated clinically with other prescriptions contained Mahuang. So, it is reasonable to believe that the traditional use of Mahuang will play an even greater role in addressing the challenges of various diseases than ever before.

Compared to Mahuang, the research and application of Mahuanggen is much less. Mahuanggen is sweet and has a warm nature, and it belongs to lung meridians that can strengthen exterior and reduce sweating. According to the records in many ancient Chinese medical books, Mahuanggen is widely used to relieve night sweating, spontaneous sweating, and depress blood pressure [13].

It is due to flexible and diverse processing methods and the use of monarch, minister, assistant and guide in traditional Chinese medicine prescription, Mahuang or Mahuanggen, can comprehensively regulate the body state and exhibit less toxicity compared with western medicine treatment. However, the mechanism behind its curative effect remain unclear, so much attention should be paid to the research of medicinal mechanism behind Mahuang and Mahuanggen.

Progress in Modern Pharmacology

In addition to traditional use, the bioactivities of extracts and monomeric compounds from *Ephedra* herbs have also been explored and tested. With the development of chemical extraction and separation technology, more active constituents of *Ephedra* herbs are increasingly extracted and identified. Likewise, the molecular mechanism underlying the pharmacological activities of *Ephedra* herbs has also been gradually clarified, which is largely beneficial from the progress of contemporary evidence-based medicine and molecular biology technology. The modern pharmacologies of *Ephedra* herb are shown in Table 1.

Antipyretic, diaphoretic and antisudorific effects

There were few studies about the antipyretic effect of *Ephedra* herb, and its antipyretic efficacy is slow and week. Wang *et al*. [14] established a rat fever model by dry yeast and found that that *Ephedra* herbs exert an antipyretic effect on the basis of its alkaloids, volatile oils, and phenolic acids from stems. Comparing with antipyretic effect, diaphoretic effect is more remarkable from *Ephedra* herb which works by impeding sodium ion reabsorption in sudoriferous ducts, and its efficacy is supported by active ingredients as following: alkaloids, water extracts, alcohol extracts, and volatile oils [15]. Except for the substances mentioned above, Ephedrans polysaccharide (ESP) from *Ephedra* stem was also confirmed to induce sweeting in mice. The study showed that there was positive correlation between diaphoretic degree and ESP dose from 66 to 132 $mg\cdot kg^{-1}$, which exhibited a significant difference compared with negative control ($P < 0.01$) [16].

Contrary to the pharmacological actions of *Ephedra* stem, the pharmacological actions of alkaloids extracted from *Ephedra* root can inhibit the symptoms of sweating caused by hypothermia and nicotine, which are often used as an antiperspirant in clinics. Latest pharmacological studies have confirmed that being an effective component derived from *Ephedra* root, mahuannin B is plays an important role in the antisudorific process, and it ultimately exerts antisudorific effects by inhibiting the normal function of the β2-adrenoceptor/cyclic adenosine monophosphate signaling pathway ($IC_{50} = 0.27$ $\mu mol\cdot L^{-1}$) [17].

Regulate blood pressure

Except for their role in the regulation of sweating secretion, *Ephedra* stem and root also have opposite effects on regulating blood pressure due to the differences in chemical compositions, which are considered to be the special function of *Ephedra* herbs; this phenomenon is a rare case in all botanicals. Studies have shown that Ephedrine and its hydrochlorides in stems are commonly used to treat hypotension caused by subarachnoid and epidural anesthesia. However, in addition to maokonine [18], other common alkaloids in *Ephedra* root have antihypertensive effects. It appears that macrocyclic spermine alkaloids are the main components with antihypertensive effects, among which ephedradine B has the strongest effect mainly by blocking the ganglia [19]. Epiafzelechin, a common flavanol, is another active ingredient in *Ephedra* root with antihypertensive activity that can significantly reduce systolic and diastolic blood pressure [13]. Besides, researches have also confirmed that polysaccharides of *Ephedra* fruits have antihypertensive effects [20].

Cough and asthma relief

Many reports indicate that *Ephedra* herb has a mild and long-lasting anti-asthmatic effect, which is mainly attributed to alkaloids and ESP, but the underlying action mechanism is different from each other. Alkaloids exert the anti-asthmatic effects through promoting the release of neurotransmitters, such as norepinephrine and adrenaline. While alkaloids can also directly stimulate β-adrenoceptor and α-adrenergic receptor to relax the bronchial smooth muscle, and contract

Table 1 The modern pharmacological effects of *Ephedra* plants

Pharmacological effects	*Ephedra* Species	Medicinal parts/ingredients	Research object	Doses/concentrations	References
Antipyretic	ES	Stems Alkaloids	Wistar rat	$0.027\ g\cdot kg^{-1}$	[14]
	ES	Stems Volatile oils	Wistar rat	$1.35 \times 10^{-5}\ mL\cdot kg^{-1}$	[14]
	ES	Stems Phenolic acids	Wistar rat	$1.27\ g\cdot kg^{-1}$	[14]
Diaphoretic	ES	Stems Alkaloids	SD rat	$7\ g\cdot kg^{-1}$	[14]
	ES	Stems Volatile oils	SD rat	$7\ g\cdot kg^{-1}$	[15]
	ES	Stems Aqueous extracts	SD rat	$7\ g\cdot kg^{-1}$	[15]
	ES	Stems Alcohol extracts	SD rat	$7\ g\cdot kg^{-1}$	[15]
	ES	Stems ESP	Swiss mice	$66–132\ mg\cdot kg^{-1}$	[16]
Antisudorific	ES	Roots Mahuannin B	Swiss mice	$IC_{50} = 0.27\ \mu mol\cdot L^{-1}$	[17]
Increasing blood pressure	*Ephedra*	Stems Ephedrine hydrochlorides			[18]
Hypotensive	*Ephedra*	Roots –Ephedradine A	Wistar rat	$3\ mg\cdot kg^{-1}$	[19]
	Ephedra	Roots Ephedradine B	Wistar rat	$3\ mg\cdot kg^{-1}$	[19]
	Ephedra	Roots Ephedradine C	Wistar rat	$3\ mg\cdot kg^{-1}$	[19]
	Ephedra	Roots Ephedradine D	Wistar rat	$3\ mg\cdot kg^{-1}$	[19]
	Ephedra	Roots Epiafzelechin	Spontaneously hypertensive rat	$10\ mg\cdot kg^{-1}$	[13]
	ES	Polysaccharides of fruits	Rabbit	$5\ mL\cdot kg^{-1}$	[20]
Cough and asthma relief	ES	Stems Alkaloids			[21]
	ES	Stems Polysaccharides	Swiss mice	$66–132\ mg\cdot kg^{-1}$	[16]
	ES	Stems Tetramethylpyrazine			[22]
	ES	Stems L-α-terpineol			[22]
	ES	Aqueous extract parts	BALB/c mice	$1\ g\cdot mL^{-1}$	[23]
Diuretic	*Ephedra*	Stems D-pseudoephedrine	Anesthetic dogs	$0.5–1.0\ mg\cdot kg^{-1}$	[24]
	Ephedra	Stems Eephedrine			[25]
	ES	Stems Alkaloids	SD rat	$0.02\ g\cdot kg^{-1}$	[26]
Excitatory central nerve	*Ephedra*	Phenylalkylamine alkaloids			[27]
	Ephedra	xanthine			[27]
Improving memory	*Ephedra*	Methylephedrine	Swiss mice	$200\ mg\cdot kg^{-1}$	[28]
Analgesic effects	*Ephedra*	Stems Ephedrine, pseudoephedrine	ICR mice	$6–12\ mg\cdot kg^{-1}$	[30]
	ES	EFE	ICR mice	$350–700\ mg\cdot kg^{-1}$	[31]
Anti-inflammatory	*Ephedra*	Stems Pseudoephedrine	Mice	$100–200\ mg\cdot kg^{-1}$	[32]
	Ephedra	Stems Ephedrine	Mice	$100–200\ mg\cdot kg^{-1}$	[32]
	Ephedra	Stems Pseudoephedroxane	Mice	$100–200\ mg\cdot kg^{-1}$	[32]
	Ephedra	Stems Ephedroxane	Mice	$100–200\ mg\cdot kg^{-1}$	[32]
	ES	Roots Ephedradine A	RAW 264.7 cells	$72\ \mu mol\cdot L^{-1}$	[33]
	ES	Roots Ephedradine B	RAW 264.7 cells	$7.2\ \mu mol\cdot L^{-1}$	[33]
	EG[b]	Stems Aqueous fraction	SD rat	$200\ mg\cdot kg^{-1}$	[34]
	Ephedra	EFE	Wistar rat		[35]
Anti-immunity	*Ephedra*	ESP	EAT mice	$33–66\ mg\cdot kg^{-1}$	[36]
	ES	Mahuang-9905	BALB/c mice	$3.7\ mg\cdot d^{-1}$	[37]

Continued

Pharmacological effects	*Ephedra* Species	Medicinal parts/ingredients	Research object	Doses/concentrations	References
	ES	CIC	Wistar rat	12 mg·kg^{-1}	[39]
Anti-cancer	ES	Herbacetin			[2]
	ES	Roots Ephedrannin A	B16F10 murine melanoma cells	72 μmol·L^{-1}	[41]
	ES	Roots Ephedrannin B	B16F10 murine melanoma cells	7.4 μmol·L^{-1}	[41]
	ES	Roots Ephedrannin B	HeLa cells	IC_{50} = 8.5 μg·mL^{-1}	[43]
	ES	Roots Ephedrannin B	Gastric cancer cell-7901	IC_{50} = 10 μg·mL^{-1}	[43]
	ES	Roots Ephedrannin B	Hepatocarcinoma cell-2	IC_{50} = 10.2 μg·mL^{-1}	[43]
	ES	EFE	MDA-MB-231 cells	40 μg·mL^{-1}	[31]
	Ephedra	EFE	H1975 NSCLC cell line	IC_{50} = 76 μg·mL^{-1}	[44]
Antimicrobial	EST[d]	Methanolic extracts			[45]
	EP[e]	Methanolic extracts			[45]
	EPA[f]	Methanolic extracts			[45]
	ES	L-*α*-terpineol			[22]
	ET[g]	Transtorine	Patients	MIC = 0.02 mg·mL^{-1}	[46]
	Ephedra	Stems/seeds *cis*-3,4-methanoproline			[47]
	EPA	Stems Quinaldic acid			[48]
	ES	Stems A-type proanthocyanidins	Bacteria	MIC = 0.00515–1.38 mmol·L^{-1}	[49]
Antiviral activity	ES	EFE	Madin–Darby canine kidney cells	IC_{50} = 8.3 μg mL^{-1}	[31]
Antioxidant	EA[h]	Phenols		IC_{50} = 78 μg·mL^{-1}	[50]
	Ephedra	Quercetin	DPPH radical	IC_{50} = 8.9 μmol·L^{-1}	[51]
	Ephedra	rutin	DPPH radical	IC_{50} = 11.1 μmol·L^{-1}	[51]
	Ephedra	gallocatechin	DPPH radical	IC_{50} = 6.9 μmol·L^{-1}	[51]
	ES	Tetramethylpyrazine	DPPH radical	IC_{50} = 126.8 ± 2.3 μg·mL^{-1}	[52]
	ES	l-*α*-terpineol	DPPH radical	IC_{50} = 94.6 ± 1.0 μg·mL^{-1}	[52]
Hypoglycemic activity	ED[i]	Ephedran A	Normal mice	100 mg·kg^{-1}	[53]
	ED	Ephedran B	Normal mice	100 mg·kg^{-1}	[53]
	ED	Ephedran C	Normal mice	100 mg·kg^{-1}	[53]
	ED	Ephedran D	Normal mice	100 mg·kg^{-1}	[53]
	ED	Ephedran E	Normal mice	100 mg·kg^{-1}	[53]
	EA	Acrial parts	Wistar rat	100 mg·kg^{-1}	[54]
Anti-hyperlipemia effect	*Ephedra*	EFE			[55]
Skin diseases	ES	Extract	HaCaT cells		[56]
	EPA	Extract	SW1 mice	140–1400 mg·kg^{-1}	[57]
Anticoagulant effect	ES	Polysaccharides of fruits	Rabbit	200 mg·kg^{-1}	[58]

[a] *Ephedra* sinica; ESP: *Ephedra* polysaccharides; IC_{50}, half maximal inhibitory concentration; [b] *Ephedra gerardiana*; EFE, Ephedrine alkaloids-free ephedra; [c] *Ephedra intermedia*; CIC, complement inhibiting component; NSCLC, Non-small-cell lung carcinoma; [d] *Ephedra strobiliacea*; [e] *Ephedra procera*; [f] *Ephedra pachyclada*; MIC, minimum inhibitory concentration; [g] *Ephedra transitoria*; [h] *Ephedra alata*; DPPH, 1, 1-diphenyl-2-picrylhydrazyl; [i] *Ephedra distachya*

peripheral blood vessels to eliminate bronchial mucosal swelling, respectively. In addition to act on the central nervous system, it is found that *Ephedra* alkaloids have the anti-asthmatic effects by preventing the release of allergic mediators to exert anti-inflammatory efficacy [21]. Unlike alkaloids, ESP can reduce coughing time and prolong cough latencies to treat bronchial asthma [16]. Two volatile oils obtained from steam distillation of *E. sinica*, namely tetramethylpyrazine and l-α-terpineol, also have been proved to have antiasthmatic effects, and the pharmacological activity of tetramethylpyrazine is higher than that of l-α-terpineol [22]. The research reported by Wang *et al*. [23] showed that *Ephedra* aqueous extract administered via atomization can inhibit airway inflammation and eosnophils infiltration and prevent IL interleukin-13 and eotaxin protein expression to control asthma. In comparison with oral medication, aerosolization of *Ephedra* aqueous extract may be a promising method to treat asthma with less adverse effects, which should be further promoted and applied.

Diuretic effect

It was reported that alkaloids from *Ephedra* stem have the function of clearing and regulating the distribution and excretion of water *in vivo* to exert the diuretic and antioncotic effects, and D-pseudoephedrine shows the strongest pharmacological activity among all the alkaloids. Experiment results showed that urine volume can be extended to two to five times that of pre-dose when anesthetized dogs are intravenously injected with D-pseudoephedrine (0.5–1.0 mg·kg^{-1}), and the pharmacological time of single administration can reach 30–60 min [24]. The experimental findings of Karch [25] showed that ephedrine could exert diuretic effects, and its mechanism is mainly dependent upon the stimulation of the smooth muscle of the bladder. However, there are different conclusions regarding the possible diuretic mechanism of *Ephedra* alkaloids. For example, it was reported that *Ephedra* alkaloids can expand the renal blood vessel, thereby increasing renal blood flow to exhibit diuretic effect [6]. Yet, Li *et al*. [26] believed that *Ephedra* alkaloids can inhibit sodium ion reabsorption and increase chloride and sodium ion excretion in kidney tubules, meanwhile, it can also exert diuretic effects through suppressing the expression level of aquaporins 1 and 2 in the kidney.

Central Excitatory and analgesic effects

One of the well-known pharmacological effects of *Ephedra* herbs is its action on the central nervous system. Commonly, *Ephedra* herb is often used by some people as narcotics, so its cultivation and commercialization are monitored and regulated by the Chinese government. Several constituents isolated from *Ephedra* herbs have been demonstrated to have central excitatory effect, mainly including phenylalkylamine alkaloids and xanthine [27]. More importantly, being the commonly phenylalkylamine alkaloids, methylephedrine also can excite adrenergic neurotransmitter system to improve memory acquisition, consolidation, and reproduction in mice with memory consolidation disorder induced by sodium nitrite and ethanol [28].

Due to its action on the central nervous system, and ability to activate transient receptor potential vanilloid 1 to increase the central pain threshold, *Ephedra* herb is also commonly used to relieve pain clinically. Another report believed that *Ephedra* herb can relax all kinds of smooth muscles to relieve pain and regulate blood stasis to treat congestion pain [29]. No matter what kind of analgesic mechanism it may be involved in, ephedrine and pseudoephedrine are considered to be the effective ingredients of *Ephedra* herb [30]. Although alkaloids from *Ephedra* stems are usually regarded as components that exert analgesic effects, other studies have shown that Ephedrine Alkaloids-Free *Ephedra* (EFE) (350–700 mg·kg^{-1}) can also reduce formaline-induced pain in a dose-dependent manner [31].

Anti-inflammatory effect

Modern pharmacological studies have also shown that *Ephedra* herbs play an important role in anti-inflammatory. Research revealed that alkaloids of *Ephedra* stems such as ephedrine, pseudoephedrine, ephedroxane, and pseudoephedroxane can inhibit prostaglandin E2 (PGE2) biosynthesis to exert an anti-inflammatory effect and pseudoephedrine has the strongest pharmacological activity [32]. Not only in stems, ephedrannin A and B obtained from *Ephedra* roots can also show a strong anti-inflammatory effect on lipopolysaccharide-stimulated RAW 264.7 cells by effectively inhibiting nuclear factor-κB and p38-mitogen-activated protein. However, the optimal dose of ephedrannin B (7.4 μmol·L^{-1}) was 10 times lower than that of ephedrannin A (72 μmol·L^{-1}), which indicates that ephedrannin B may be a good candidate for treating human inflammatory diseases [33].

Another study showed that the aqueous fraction of *E. gerardiana* stem has an anti-inflammatory effect, and the effect might be based primarily on its ability to decreases pro-inflammatory factors, such as PGE2, cyclooxygenase-2, interleukin (IL)-1β, IL-6, nuclear factor-κB, and tumor necrosis factor, and increases anti-inflammatory factors including IL-4 and IL-10 [34]. Additionally, EFE appears to exert an anti-inflammatory effect through inhibiting the release of histamine and increasing the level of cyclic adenosine monophosphate in basophil leukemia cell-2H3 induced by IgE [35].

Anti-immunity activity

With the deeper study of *Ephedra* herbs, it is gradually accepted that *Ephedra* herbs also have anti-immunity activities, which exhibit unique effects between specific and non-specific immunity and between cell and humoral immunity. According to reports conducted by Yan *et al*. [36], ESP (33–66 mg·kg^{-1}) is the effective constituent that exerts anti-immunity effects by regulating the level of thyroid hormones and serum antibodies and obstructing the peripheral blood lymphocyte subsets. In addition, Chen *et al*. [37] found that Mahuang-9905 extracted from *E. sinica* could inhibit ear swelling induced by dinitrochlorobenzene in mice, and confirmed that this phenomenon was caused by its anti-immunity effects, and the authors indicates that the mechanism may be related to the atrophy of thymus gland and the decrease of T lymphocyte formation.

Since 1989, an effective complement-inhibiting component of *Ephedra* herbs was obtained [38], later, many researchers found that it is an effective component with anti-immunity effect used in many immunological diseases. For example, it can delay the progression of acute rejection, and prolong the survival time of transplanted hearts for heart xenotransplantation [39]. Another report showed that it inhibited the activities of myeloperoxidase and the mRNA expression level of intercellular adhesion molecule-1 to ease immune inflammatory response after spinal cord injury [40].

Anti-cancer activity

It was reported that herbacetin extracted from the stem of *E. sinica* can inhibit the mobility of human breast cancer induced by hepatocyte growth factor through inhibiting the proliferation of malignant cells and suppressing of c-Met tyrosine phosphorylation [2]. Additionally, ephedrannin A and B from root of *E. sinica*, can slow the growth of melanoma B16-F10 cells, and reduce melanin production in cells, which results in depigmentation of the skin [41]. As a commonly dimer tannins of *Ephedra* herbs, ephedrannin B also has a certain degree of inhibition on the growth of HeLa cells (IC_{50} = 8.5 μg·mL^{-1}), gastric cancer cell-7901 (IC_{50} = 10 μg·mL^{-1}), and hepatocarcinoma cell-2 (IC_{50} = 10.2 μg·mL^{-1}) [42, 43]. Clinically, Hyuga *et al*. [31] demonstrated that EFE (40 μg·mL^{-1}) suppressed the phosphorylation induced by hepatocyte growth factor in human breast cancer cell MDA-AB-231, it (IC_{50} = 76 μg·mL^{-1}) also can resist non-small cell lung cancer cell lines H1975 proliferation for the treatment of lung cancer [44]. In sum, accumulated reports have shown that *Ephedra* herb could treat various cancers, and thereby as a famous age-old herb, *Ephedra* herb is a new choice for the treatment of cancer. Yet, the anticancer effects of *Ephedra* herb have been characterized insufficiently, and more pharmacological and mechanistic investigations are required.

Antimicrobial activity

Ephedra herb appears to have potent inhibitory activity against bacteria and fungi. Parsaeimehr *et al*. [45] conducted a research of antimicrobial activity of three species of *Ephedra* using the disc diffusion method, and the results showed that methanolic extracts of all *Ephedra* species showed antimicrobial activity against common microorganism such as *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Colibacillus* spp., *Klebsiella* spp., *Candida albicans*, and *Aspergillus* spp. Compared with *E. procera* and *E. pachyclada*, methanolic extracts of *E. strobilacea* showed the highest efficacy. In addition to methanolic extracts, some other monomeric compounds are also confirmed to have anti-bacterial effect. In 1983, Sun conducted a bacteriostasis experiment in which l-*α*-Terpineol extracted from *E. sinica* stem could inhibit the growth of *Bacillus paratyphosus* and *Staphylococcus aureus* [22]. Later, transtorine (MIC = 0.02 mg·mL^{-1}) isolated from the aerial part of *E. transitoria* and *cis*-3,4-methanoproline existed in the stems and seeds of many *Ephedra* species also have a certain degree of anti-bacterial effect [46, 47]. In addition, quinaldic acid derived from the stems of *E. pachyclada* can be mainly used against intestinal bacteria, such as *Clostridium difficile* and *Clostridium perfringens*, and it showed a strong inhibition at 1.0 mg·disc^{-1} [48]. Not only that, Zang *et al*. [49] found 12 new A-type proanthocyanidins from *E. sinica* stem, which were also confirmed to have different levels of bacteriostatic effects determined by a serial dilution technique using 96-well microtiter plates, with an MIC ranging from 0.00515 to 1.38 mmol·L^{-1}. Also, EFE can inhibit influenza virus infection in Madin–Darby canine kidney (IC_{50} = 8.3 μg·mL^{-1}) [31].

There have been many investigations into the antimicrobial and antirival activity of *Ephedra* herb, and the effective substances are mainly tannins, volatile oils, organic acids, and other non-alkaloids substances from *Ephedra* herb. Compared with antibiotics, the substances mentioned above have fewer side effects, so further research is needed to expand their utility in the development of new antibacterial and antiviral therapies.

Antioxidant activity

When exploring the content of phenolic compounds of *E. alata* and their antioxidant activity, researchers found that there was a significant relation between phenolic compounds (IC_{50} = 78 μg·mL^{-1}) and antioxidant activity. The mechanism seems to be associated with the reactive hydrogen or electron-donating groups that can scavenge diphenyl-p-picrylhydrazyl free radicals [50]. Additionally, flavonoids from *Ephedra* herb, such as quercetin (IC_{50} = 8.9 μmol·L^{-1}), rutin (IC_{50} = 11.1 μmol·L^{-1}), and gallocatechin (IC_{50} = 6.9 μmol·L^{-1}), also have antioxidant effects, and result showed that the antioxidant capacity of isoflavones is weaker than that of flavonoids [51]. In addition to phenolic compounds and flavonoids, two volatile oils, namely, tetramethylpyrazine (IC_{50} = 126.8 ± 2.3 μg·mL^{-1}) and l-α-terpineol (IC_{50} = 94.6 ± 1.0 μg·mL^{-1}) also were found to have a significant antioxidant activity [52]. As a natural source of potent antioxidants, these effective compounds of *Ephedra* herbs may prevent many diseases and could be potentially used in food, cosmetics, and pharmaceutical products to delay senescence and keep body health.

Other pharmacological effects

In addition to the common pharmacological activities described above, *Ephedra* herbs also have other pharmacological effects. It was reported that ESP A, B, C, D, and E (100 mg·kg^{-1}) derived from *E. distachya* stem are effective in lowering blood glucose, and among them, ESP C has the strongest hypoglycemic activity [53]. Moreover, the aerial part of *E. alata* was also confirmed to significantly inhibit *α*-amylase and *α*-glucosidase activities and reduce the blood glucose level in the body, but the hypoglycemic effect of its active ingredient is unknown yet [54]. Not only can treat hyperglycemia, the experimental findings showed that *Ephedra* herb also has an anti-hyperlipemia effect which may be due to EFE. The possible underlying mechanisms are significant reduction of total triglyceride and total cholesterol levels, increase in high-density lipoprotein levels, reduction of glutamic-pyruvic transaminase and glutamic oxalacetic transaminase activities, and accelerated lipids metabolism [55]. It is also confirmed that *Ephedra* extracts can not only treat skin inflammation and photoaging by inhibiting gene expressions of Ultraviolet B-induced cyclooxygenase-2 and matrix metalloproteinase, and also alleviate acute and chronic liver damage through inhibiting oxidative stress and reducing inflammatory molecules *in vivo* [56, 57]. Additionally, reports have suggested that polysaccharides of *Ephedra* fruits exert anticoagulant effects through two internal and external coagulation pathways [58].

Ephedra Herbs Used as a Dietary Supplement and Its Adverse Reaction

In many countries, such as the United States, South Korea, and parts of Asia, ephedrine-containing herbal complexes are commonly used as dietary supplements due to the sympathetic activity of *Ephedra* herb, which can also alter the intestinal flora of people with obesity [59]. *Ephedra* herb has also become an effective drug to improve an athlete's physical performance by increasing metabolism and fatigue remission in the body. Therefore, *Ephedra* dietary supplements and performance-enhancing drugs were popular in the 1980s [25, 60]. Low-dose *Ephedra* extracts can reduce weight in a short period and improve athletes' physical performance. However, high dose or long-term use of *Ephedra* extracts can cause various adverse effects, such as anxiety, insomnia, palpitations, arrhythmia, and even death [61, 62]. In view of a rule issued by FDA in 2004, saying that the sale of dietary supplements containing *Ephedra* alkaloids is prohibited, so, the medicinal development of *Ephedra* alkaloids will be hindered to some extent [25].

Overview of Chemical Studies on *Ephedra* Herb

Like other herbs, the pharmacological activities of *Ephedra* herbs are mainly determined by their various chemical constituents. To date, more and more pharmacologically active chemical ingredients, such as alkaloids, flavonoids, tannins, polysaccharides, volatile oils, and organic acids, have been thoroughly understood and have considerably promoted the extensive application of *Ephedra* herbs. At present, it is reported that at least 247 chemical components, including 29 alkaloids, 52 flavonoids, 48 tannins, 28 organic acids, 13 polysaccharides, 31 volatile oils, and 46 other compounds, such as anthraquinones, phenols, and nucleic acids, have been found from *Ephedra* herbs.

Alkaloids

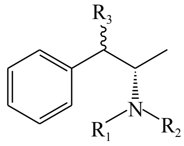
Alkaloids are the first active ingredients found in *Ephedra* herb and have been used as a standard for evaluating the quality of *Ephedra* herb. In 1885, Nagai isolated ephedrine from *Ephedra* herb [63]. Phenylalkylamine alkaloids are common active products in *Ephedra* stems, and the most common alkaloids are l-ephedrine (**1**), l-methylephedrine (**3**), l-norephedrine (**5**), and their isomers (**2**, **4** and **6**). Macrocyclic spermine alkaloids, such as ephedradine A, B, C, and D (**18**–**21**), mostly constitute the roots of *Ephedra* herb [64]. In addition, feruloylhistamine (**16**) and maokonine (**17**) belonging to phenylalkylamine alkaloids were separated from *Ephedra* roots with different regulating activity in the blood pressure [18, 65]. Kasahara *et al*. (1985) isolated ephedroxane (**22**) from the aerial parts of *E. intermedia*, and other scholars obtained two ephedroxane derivatives (**23**–**24**) and five quinolines (**25**–**29**) from different species of *Ephedra* [66, 67]. The chemical structures of these alkaloids (**1**–**29**) are shown in Fig. 2. The specific names, sources, chemical formulas, molecular weights, and other information on alkaloids are shown in Table 2.

Flavonoids

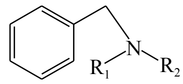
Flavonoids are important components of *Ephedra* herbs, approximately 0.29% mass of the plant are flavonoids, dihydroflavonoids, flavonols, dihydroflavonols, flavanols, and anthocyanins [6]. Flavonoids are mostly derived from apigenin (**30**), luteolin (**35**), vitexin (**37**), and their glycoside derivatives; flavonols are mainly derived from kaempferol (**45**), quercetin (**51**), herbacetin (**55**), and glycoside derivatives. On the basis of structural formulas, we can conclude that flavonoids from *Ephedra* herbs are mostly substituted with 3, 3′, 4′, 5, 7, and 8 hydroxy groups in the flavonoids' basic skeleton. The aglycones of glycosidic derivatives are mainly composed of glucose and rhamnose and a small number of mannose and neohesperidoside; flavanols are mainly catechin (**66**) and afzelechin (**70**). The chemical structures of these flavonoids (**30**–**81**) are shown in Fig. 2. The detailed information about flavonoids is shown in Table 2.

Tannins

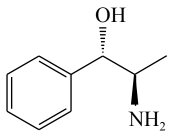
Tannins in *Ephedra* herb are mostly condensed and presented as dimers, trimmers and tetramers, and they are mainly composed of epigallocatechin and catechin [49]. Most dimer tannins are composed of two flavanols, including catechin, epicatechin, gallocatechin, epigallocatechin, afzelechin, and epiafzelechin. These compounds are usually connected by C2–C7 and C4–C8 (**84**–**100**), and isoflavanols are connected to C3–C7 (**105**–**106**). Stereoisomerism in a joint space has produced different compounds. In addition, several compounds are composed of flavonols and other types of flavonoids (**82**–**83**, **103**–**104**, and **107**–**108**), whereas muhuannin D (**101**) and muhuannin E (**102**) are composed of flavanoids and flavanols. Trimeric tannins are composed of three flavanols. Every two flavanols are connected by a single bond or a double bond, and most of them occur at C2–C7 and C4–C8 and are spatially isomeric at the connection (**109**–**116**, **119**–**123**). Special ephedrannin Tr9 (**117**) and ephedrannin Tr10 (**118**) are connected by C4–C6. Tetrameric tannins (**124**–**128**) are also polymerized from four flavanols linked together in the same way as most trimer tannins. In addition, hydrolytic tannin nilocitin (**129**) has been isolated from *E. alata* herb via ethanol extraction [68]. The tannin forms of *E. americana* are different in caulicle and woody stems, and tannins exist as prodelphinidin polymer in the former, while they



1 $R_1 = H, R_2 = CH_3, R_3 =$ ◀OH
2 $R_1 = H, R_2 = CH_3, R_3 =$ ···OH
3 $R_1 = R_2 = CH_3, R_3 =$ ◀OH
4 $R_1 = R_2 = CH_3, R_3 =$ ···OH
5 $R_1 = R_2 = H, R_3 =$ ◀OH
6 $R_1 = R_2 = H, R_3 =$ ···OH



7 $R_1 = R_2 = H$
8 $R_1 = CH_3, R_2 = H$



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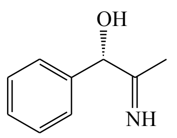

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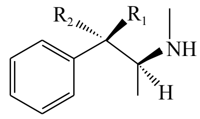
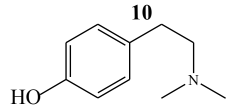


11 $R_1 = OOCC_6H_5, R_2 = H$
12 $R_1 = H, R_2 = OOCC_6H_5$



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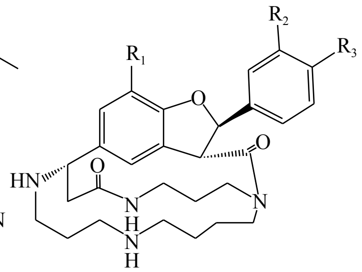
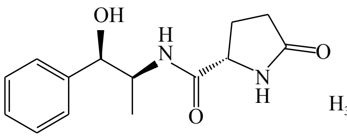


18 $R_1 = R_2 = H, R_3 = OH$
19 $R_1 = H, R_2 = OCH_3, R_3 = OH$
20 $R_1 = H, R_2 = R_3 = OCH_3$
21 $R_1 = OCH_3, R_2 = H, R_3 = OH$



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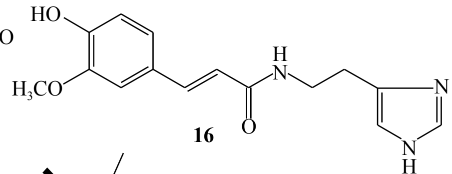

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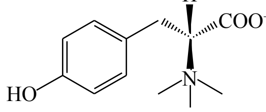

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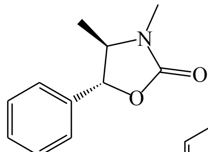

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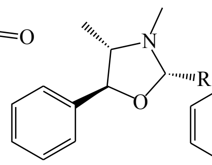
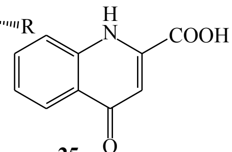


23 R = H
24 $R = CH_3$



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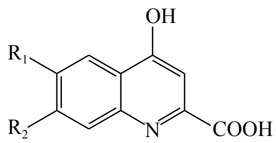
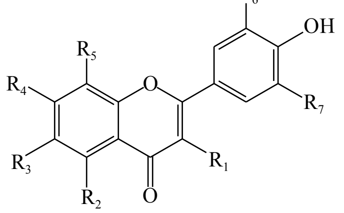
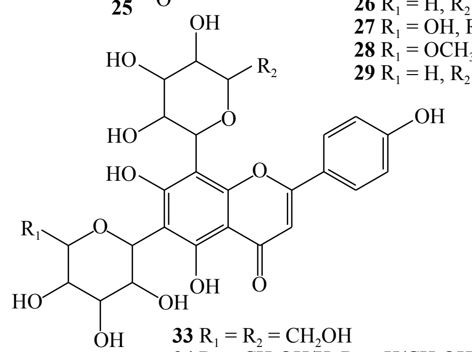


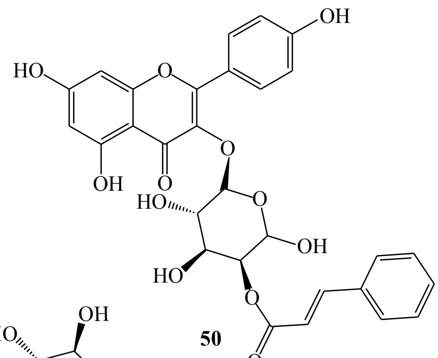
26 $R_1 = H, R_2 = H$
27 $R_1 = OH, R_2 = H$
28 $R_1 = OCH_3, R_2 = H$
29 $R_1 = H, R_2 = OCH_3$



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
30	H	OH	H	OH	H	H	H
31	H	OH	H	OGlu	H	H	H
32	H	ORha	H	OH	H	H	H
35	H	OH	H	OH	H	OH	H
36	H	OH	H	OGlu	H	OH	H
37	H	OH	H	OH	Glu	H	H
38	H	OH	Glu	OH	H	H	H
39	H	OH	H	OH	Glu-2-O-Rha	H	H
40	H	OH	Glu-2-O-Rha	OH	H	H	H
41	H	OH	2Glu	OH	2Glu	OCH_3	H
42	H	OH	Glu	OH	Xy1	H	OH
43	H	OH	Glu	OH	H	OCH_3	H
44	H	OH	H	OH	H	OCH_3	OCH_3
45	OH	OH	H	OH	H	H	H
46	OGlu	OH	H	ORha	H	H	H
47	ORha	OH	H	OGlu	H	H	H
48	ORha	OH	H	OH	H	H	H
49	OH	OH	H	ORha	H	H	H
51	OH	OH	H	OH	H	OH	H
52	OGlu	OH	H	OH	H	OH	H
53	ORha	OH	H	OH	H	OH	H
54	OGla	OH	H	OH	H	OH	H
55	OH	OH	H	OH	OH	H	H
56	OCH_3	OH	H	OH	OH	H	H
57	OH	OH	H	OCH_3	OH	H	H
58	OH	OH	H	OGlu	OH	H	H
60	OGlu	OH	H	OH	OCH_3	H	H
61	ORha	OH	H	OH	OGlu	H	H
62	OGlu	OH	H	ORut	OCH_3	H	H
63	OH	OH	H	ONeo	OH	H	H
64	ORut	OH	H	OH	H	OH	H



33 $R_1 = R_2 = CH_2OH$
34 $R_1 = CH_2OH/H, R_2 = H/CH_2OH$



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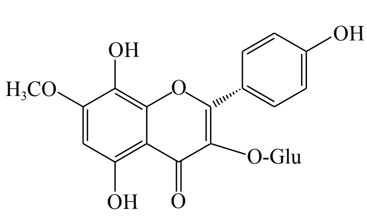

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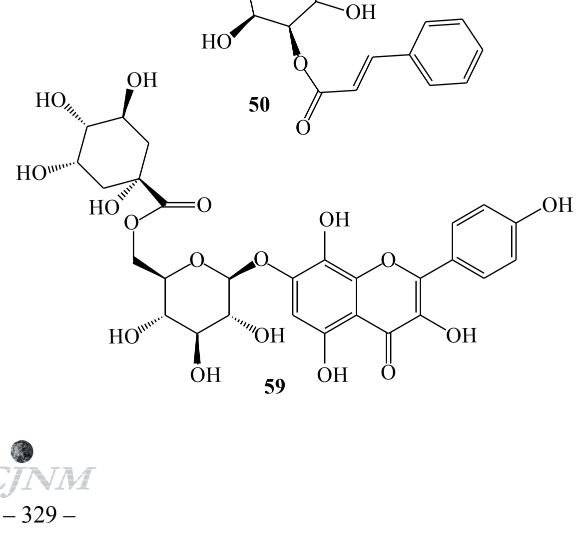

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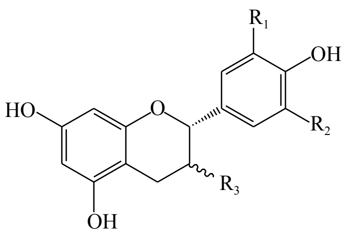
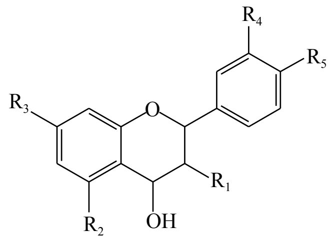
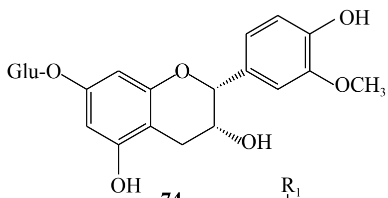


66 R_1 = OH, R_2 = H, R_3 = OH
67 R_1 = OH, R_2 = H, R_3 = OH
68 R_1 = R_2 = OH, R_3 = OH
69 R_1 = R_2 = OH, R_3 = OH
70 R_1 = R_2 = H, R_3 = OH
71 R_1 = R_2 = H, R_3 = OH



72 R_1 = R_2 = R_3 = R_4 = R_5 = OH
73 R_1 = OH, R_2 = R_3 = R_4 = R_5 = H



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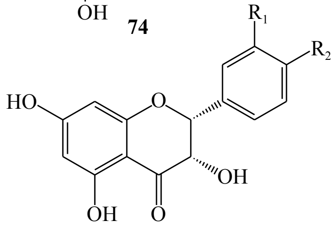
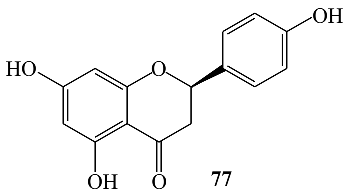


75 R_1 = H, R_2 = OH
76 R_1 = R_2 = OH



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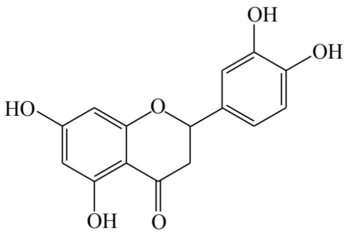

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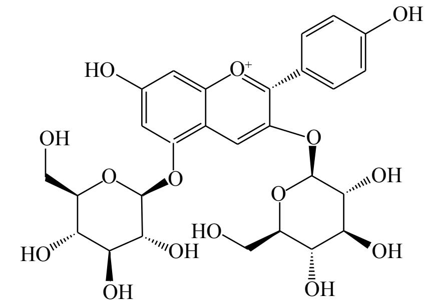

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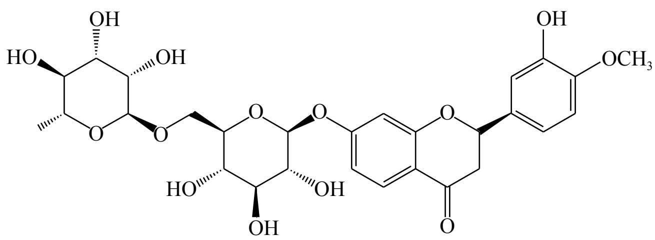

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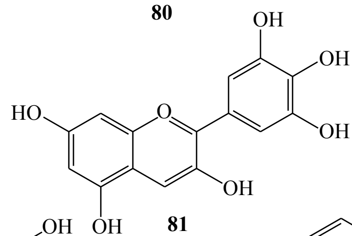

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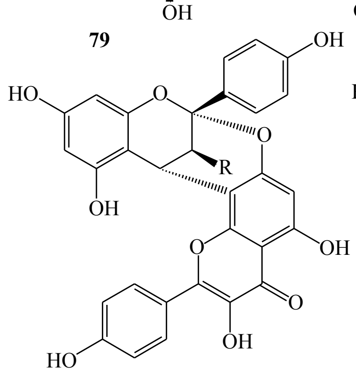
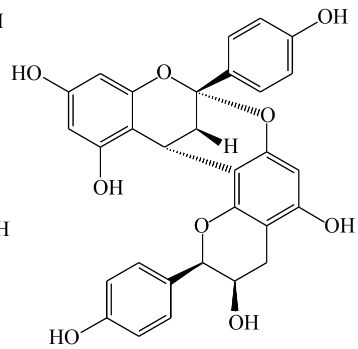


82 R = OH
83 R = H



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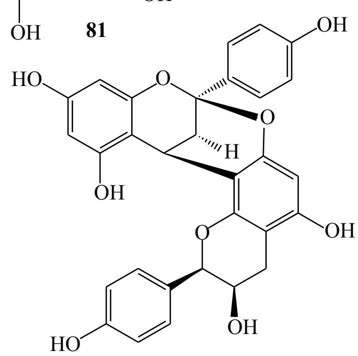

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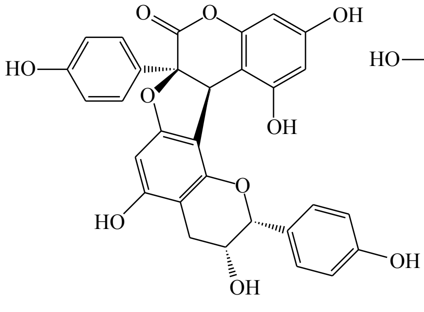

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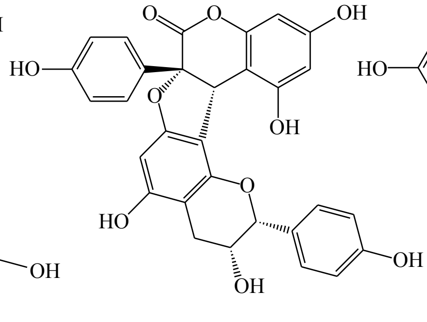

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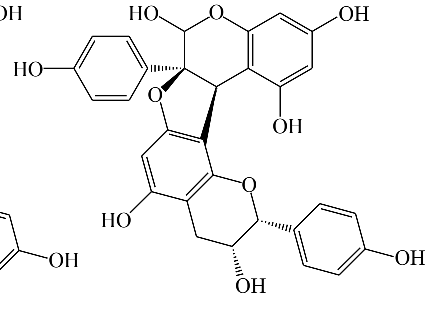

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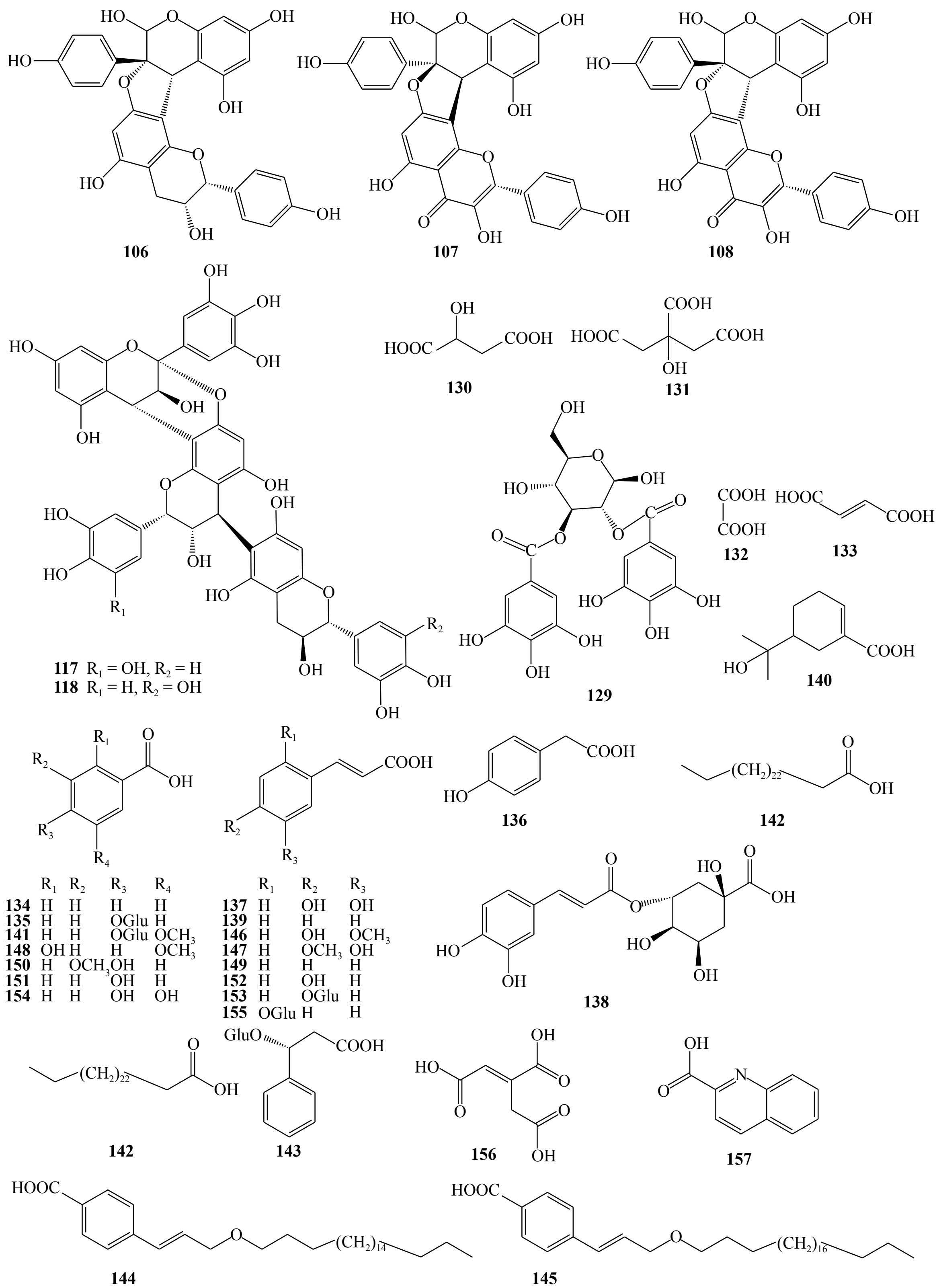


Fig. 2 The chemical structures of alkaloids, flavonoids, tannins, and organic acids from *Ephedra* plants

exist as proanthocyanidin polymers in the latter [69]. Information (**82–129**) on their identity is shown in Table 2. The chemical structures of characteristic tannins (**82–83**, **101–108**, **117–118**, and **129**) are shown in Fig. 2.

Organic acids

Organic acids are also the characteristic constituents of *Ephedra* herbs, and they are widely distributed in different *Ephedra* parts. For the past few years, 27 organic acids

Table 2 The information of alkaloids, flavonoids, tannins and organic acids from *Ephedra* plants

No.	Structural category	Name	Species	PP	CF	FW	References
1	Phenylalkylamine-type alkaloids	L-Ephedrine	ES[a]	Herbs	$C_{10}H_{15}NO$	165.23	[81]
2		D-Pseudoephedrine	ES	Herbs	$C_{10}H_{15}NO$	165.23	[81]
3		L-Methyephedrine	ES	Herbs	$C_{11}H_{17}NO$	179.26	[81]
4		D-Methylpseudoephedrine	ES	Herbs	$C_{11}H_{17}NO$	179.26	[85]
5		L-Norephedrine	ES	Herbs	$C_9H_{13}NO$	151.21	[85]
6		D-Norpseudoephedrine	ES	Herbs	$C_9H_{13}NO$	151.21	[85]
7		Benzylamine	ES	Stems	C_7H_9N	107.00	[86]
8		*N*-Methyl benzylamine	ES	Stems	$C_8H_{11}N$	121.18	[87]
9		Phenylpropanolamine	ES	Stems	$C_9H_{13}NO$	151.00	[81]
10		(±)-1-phenyl-2-imido-1-propanol	ES	Stems	$C_9H_{11}NO$	149.00	[74]
11		*O*-benzoyl-L-ephedrine	ES	Stems	$C_{17}H_{19}NO_2$	269.00	[88]
12		*O*-benzoyl-D-pseudoephedrine	ES	Stems	$C_{17}H_{19}NO_2$	269.00	[88]
13		(*S*)-*N*-((1*R*, 2*S*)-1-hydroxy-1-phenylprop an-2-yl)-5-oxopyrrolidine-2-carboxamide	ES	Stems	$C_{14}H_{18}N_2O_3$	262.14	[89]
14		Ephedine	ES	Stems	—	—	[82]
15		Hordenine	EA[b]	Aerial parts	$C_{10}H_{15}NO$	165.12	[90]
16		Feruloylhistamine	*Ephedra* sp.	Roots	$C_{15}H_{17}N_3O_3$	287.12	[64]
17		Maokonine	ES	Roots	$C_{12}H_{17}NO_3$	223.00	[18]
18	Macrocyclic spermine alkaloids	Ephedradine A	ES	Herbs	$C_{28}H_{36}N_4O_4$	492.28	[91]
19		Ephedradine B	ES	Roots	$C_{29}H_{38}N_4O_5$	522.29	[91]
20		Ephedradine C	ES	Roots	$C_{30}H_{40}N_4O_5$	536.00	[19]
21		Ephedradine D	ES	Roots	$C_{29}H_{38}N_4O_5$	522.29	[91]
22	Oxazolidine alkaloids	Ephedroxane	EI[c]	Aerial parts	$C_{11}H_{13}NO_2$	191.00	[92]
23		3, 4-dimethyl-5-pheyloxazolidine	ES	Stems	$C_{11}H_{15}NO$	177.00	[67]
24		2, 3, 4-trimethyl-5-phenyloxazolidine	ES	Stems	$C_{12}H_{17}NO$	191.00	[67]
25	Quinoline alkaloids	Transtorine	ET[d]	Aerial parts	$C_{10}H_7NO_3$	189.17	[46]
26		Kynurenic acid	EPSS[e], ES	Stems	$C_{10}H_7NO_3$	189.17	[66]
27		6-hydroxykynurenic acids	EFOE[f], EFOL[g]	Stems	$C_{10}H_7NO_4$	205.00	[66]
28		6-methoxykynurenic acid	EPSS, ES	Stems	$C_{11}H_9NO_4$	219.00	[66]
29		Ephedralone	EAL[h]	Herbs	$C_{11}H_9NO_4$	219.00	[68]
30	Flavonoids	Apigenin	ES	Roots	$C_{15}H_{10}O_5$	270.24	[93]
31		Apigenin-7-glucoside	EC[i]	Stems	$C_{21}H_{20}O_{10}$	432.24	[88]
32		Apigenin-5-rhamnoside	ES	Aerial parts	$C_{21}H_{20}O_9$	416.24	[94]
33		6, 8-di-C-hexosyl apigenin	ES	Herbs	$C_{27}H_{30}O_{15}$	594.16	[91]
34		6/8-C-hexosyl-8/6-C-pentasyl apigenin	ES	Herbs	$C_{26}H_{28}O_{14}$	564.16	[91]
35		Luteolin	ES	Stems	$C_{15}H_{10}O_6$	286.23	[82]
36		Luteolin-7-glucoside	EAL	Herbs	$C_{21}H_{20}O_{11}$	448.23	[50]
37		Vitexin	ES	Stems	$C_{21}H_{20}O_{10}$	432.38	[91]

Continued

No.	Structural category	Name	Species	PP	CF	FW	References
38		Isovitexin	ES	Stems	$C_{21}H_{20}O_{10}$	432.38	[91]
39		Vitexin-2-rhamnoside	ES	Stems	$C_{27}H_{30}O_{14}$	578.00	[91]
40		Isovitexin-2-rhamnoside	ES	Aerial parts	$C_{27}H_{30}O_{14}$	578.00	[2]
41		2″ 2‴-di-*O*-*β*-glucopyranosyl-vicenin II	EA	Aerial parts	$C_{39}H_{50}O_{25}$	918.00	[95]
42		Lucenin III	EAL	Herbs	$C_{26}H_{28}O_{15}$	580.00	[96]
43		6-*C*-glycosyl-chrysoeriol	ES	Stems	$C_{22}H_{22}O_{10}$	446.00	[88]
44		Tricin	ES	Aerial parts	$C_{17}H_{14}O_{7}$	330.00	[94]
45	Flavonols	kaempferol	ES	Herbs	$C_{15}H_{10}O_{6}$	286.24	[94]
46		kaempferol-3-glucoside-7-rhamnoside	ES	Stems	$C_{27}H_{30}O_{15}$	594.00	[82]
47		kaempferol-3-*O*-rhamnoside 7-*O*-glucoside	ES	Aerial parts	$C_{27}H_{30}O_{15}$	594.00	[2]
48		Kaempferol-3-rhamnoside	EAL	Herbs	$C_{21}H_{20}O_{10}$	432.00	[96]
49		Kaempferol-7-rhamnoside	ES	Aerial parts	$C_{21}H_{20}O_{10}$	432.00	[97]
50		Kaempferol-3-*O*-*α*-L-rhamnoside-4″-*E*-hydroxyl cinnamate	ES	Stems	$C_{30}H_{26}O_{12}$	578.00	[98]
51		Quercetin	ES	Herbs	$C_{15}H_{10}O_{7}$	302.00	[93]
52		Quercetin-3-glucoside	EC	Stems	$C_{21}H_{20}O_{12}$	464.00	[88]
53		Quercetin-3-rhamnoside	EAL	Herbs	$C_{21}H_{20}O_{11}$	448.00	[96]
54		Quercetin-3-D-galactoside	ES	Stems	$C_{21}H_{20}O_{12}$	464.00	[91]
55		Herbacetin	ES	Aerial parts	$C_{15}H_{10}O_{7}$	302.24	[94]
56		3-methoxy herbacetin	ES	Aerial parts	$C_{16}H_{12}O_{7}$	316.00	[94]
57		Herbacetin-7-methylether	EA	Aerial parts	$C_{16}H_{12}O_{7}$	316.00	[95]
58		Herbacetin-7-glucoside	EL[j]	Herbs	$C_{21}H_{20}O_{12}$	464.00	[98]
59		Herbacetin-7-*O*-(6″-quinylglucoside)	EAL	Herbs	$C_{27}H_{30}O_{17}$	638.00	[96]
60		Herbacetin-8-methylether 3-glucoside	ES	Stems	$C_{22}H_{22}O_{12}$	478.00	[82]
61		Herbacetin-3-*O*-*α*-rhamnoside 8-*O*-*β*-glucoside	EA	Aerial parts	$C_{27}H_{30}O_{16}$	610.00	[95]
62		Herbacetin-8-methylether-3-*O*-glucoside-7-*O*-rutinoside	EAL	Herbs	$C_{34}H_{42}O_{21}$	786.00	[96]
63		Herbacetin-7-*O*-neohesperidoside	ES	Aerial parts	$C_{27}H_{30}O_{16}$	610.15	[2]
64		Rutin	ES	Stems	$C_{27}H_{30}O_{16}$	610.51	[82]
65		Pollenitin B	ES	Aerial parts	$C_{22}H_{22}O_{12}$	478.00	[2]
66	Flavanols	Catechin	ES	Herbs	$C_{15}H_{14}O_{6}$	290.27	[49]
67		Epicatechin	ES	Herbs	$C_{15}H_{14}O_{6}$	290.27	[49]
68		Gallocatechin	ES	Herbs	$C_{15}H_{14}O_{7}$	306.27	[49]
69		Epigallocatechin	ES	Herbs	$C_{15}H_{14}O_{7}$	306.27	[49]
70		Afzelechin	ES	Roots	$C_{15}H_{14}O_{5}$	274.00	[91]
71		Epiafzelechin	ES	Roots	$C_{15}H_{14}O_{5}$	274.00	[91]
72		Leucocyanidin	ES	Stems	$C_{15}H_{14}O_{7}$	306.27	[88]
73		leucoanthpcyanin	ES	Stems	$C_{15}H_{14}O_{3}$	242.00	[88]
74		Symplocoside	ES	Aerial parts	$C_{22}H_{26}O_{11}$	466.00	[2]
75	Flavanonols	3-hydroxy naringenin	ES	Roots	$C_{15}H_{12}O_{6}$	288.00	[77]

Continued

No.	Structural category	Name	Species	PP	CF	FW	References
76		Dihydroquercetin	ES	Roots	$C_{15}H_{12}O_7$	304.25	[93]
77	Flavonones	Naringenin	ES	Roots	$C_{15}H_{12}O_5$	272.25	[77]
78		3′, 4′, 5, 7-tetrahydroxyflavanone	ES	Roots	$C_{15}H_{12}O_6$	288.00	[93]
79		Hesperidin	ES	Stems	$C_{28}H_{34}O_{15}$	610.56	[82]
80	Anthocyans	Leucopelargonidin	ES	Stems	$C_{27}H_{31}O_{15}$	595.00	[88]
81		Leucodelphinidin	ES	Stems	$C_{15}H_{11}O_7$	303.00	[88]
82	Dimer tannins	Ephedrannin A	ES	Roots	$C_{30}H_{20}O_{11}$	556.09	[43]
83		Ephedrannin B	ES	Roots	$C_{30}H_{20}O_{10}$	540.00	[43]
84		Ephedrannin D1	ES	Stems	$C_{30}H_{24}O_{13}$	592.00	[49]
85		Ephedrannin D2	ES	Stems	$C_{30}H_{24}O_{13}$	592.00	[49]
86		Ephedrannin D3	ES	Stems	$C_{30}H_{24}O_{13}$	592.00	[49]
87		Ephedrannin D4	ES	Stems	$C_{30}H_{24}O_{14}$	608.00	[49]
88		Ephedrannin D5	ES	Stems	$C_{30}H_{24}O_{14}$	608.00	[49]
89		Ephedrannin D6	ES	Stems	$C_{30}H_{24}O_{14}$	608.00	[49]
90		Ephedrannin D7	ES	Stems	$C_{30}H_{24}O_{14}$	608.00	[49]
91		Ephedrannin D8	ES	Stems	$C_{30}H_{24}O_{14}$	608.00	[88]
92		Ephedrannin D9	ES	Stems	$C_{30}H_{24}O_{15}$	624.00	[88]
93		Ephedrannin D10	ES	Stems	$C_{30}H_{24}O_{13}$	592.00	[88]
94		Ephedrannin D11	ES	Stems	$C_{30}H_{24}O_{13}$	592.00	[88]
95		Ephedrannin D12	ES	Stems	$C_{30}H_{24}O_{13}$	592.00	[88]
96		Ephedrannin D13	ES	Stems	$C_{30}H_{24}O_{14}$	608.00	[88]
97		Ephedrannin D14	ES	Herbs	$C_{30}H_{24}O_{15}$	624.00	[88]
98		Muhuannin A	ES	Roots	$C_{30}H_{24}O_{10}$	544.00	[77]
99		Muhuannin B	ES	Roots	$C_{30}H_{24}O_{10}$	544.00	[77]
100		Muhuannin C	ES	Roots	$C_{30}H_{24}O_{10}$	544.00	[91]
101		Muhuannin D	ES	Roots	$C_{30}H_{24}O_9$	528.00	[43]
102		Muhuannin E	ES	Roots	$C_{30}H_{24}O_9$	528.00	[43]
103		Muhuannin F	ES	Roots	$C_{30}H_{22}O_{10}$	542.11	[77]
104		Muhuannin G	ES	Roots	$C_{30}H_{22}O_{10}$	542.11	[77]
105		Muhuannin H	ES	Roots	$C_{30}H_{24}O_{10}$	544.13	[77]
106		Muhuannin I	ES	Roots	$C_{30}H_{24}O_{10}$	544.13	[77]
107		Muhuannin J	ES	Roots	$C_{30}H_{20}O_{11}$	556.09	[77]
108		Muhuannin K	ES	Roots	$C_{30}H_{20}O_{11}$	556.09	[77]
109	Trimer tannins	Ephedrannin Tr1	ES	Stems	$C_{45}H_{36}O_{21}$	912.00	[49]
110		Ephedrannin Tr2	ES	Stems	$C_{45}H_{36}O_{20}$	896.00	[49]
111		Ephedrannin Tr3	ES	Stems	$C_{45}H_{36}O_{21}$	912.00	[88]
112		Ephedrannin Tr4	ES	Stems	$C_{45}H_{36}O_{21}$	912.00	[88]
113		Ephedrannin Tr5	ES	Stems	$C_{45}H_{36}O_{22}$	928.00	[88]
114		Ephedrannin Tr6	ES	Stems	$C_{45}H_{36}O_{20}$	896.00	[88]

Continued

No.	Structural category	Name	Species	PP	CF	FW	References
115		Ephedrannin Tr7	ES	Stems	$C_{45}H_{36}O_{20}$	896.00	[88]
116		Ephedrannin Tr8	ES	Stems	$C_{45}H_{36}O_{20}$	896.00	[88]
117		Ephedrannin Tr9	ES	Stems	$C_{45}H_{36}O_{20}$	896.00	[88]
118		Ephedrannin Tr10	ES	Stems	$C_{45}H_{36}O_{20}$	896.00	[88]
119		Ephedrannin Tr11	ES	Stems	$C_{45}H_{34}O_{21}$	910.00	[88]
120		Ephedrannin Tr12	ES	Stems	$C_{45}H_{34}O_{21}$	910.00	[88]
121		Ephedrannin Tr13	ES	Stems	$C_{45}H_{38}O_{21}$	914.00	[88]
122		Ephedrannin Tr14	ES	Stems	$C_{45}H_{36}O_{22}$	928.00	[88]
123		Ephedrannin Tr15	ES	Stems	$C_{45}H_{36}O_{22}$	928.00	[88]
124	Tetramer tannins	Ephedrannin Te1	ES	Stems	$C_{60}H_{46}O_{28}$	1214.00	[88]
125		Ephedrannin Te2	ES	Stems	$C_{60}H_{46}O_{28}$	1214.00	[49]
126		Ephedrannin Te3	ES	Stems	$C_{60}H_{46}O_{27}$	1198.00	[49]
127		Ephedrannin Te4	ES	Stems	$C_{60}H_{46}O_{27}$	1198.00	[49]
128		Ephedrannin Te5	ES	Stems	$C_{60}H_{46}O_{27}$	1198.00	[49]
129	Hydrolytic tannins	Nilocitin	EAL	Herbs	$C_{20}H_{20}O_{14}$	484.00	[68]
130	Organic acids	Malic acid	ES	Stems	$C_4H_6O_5$	134.09	[99]
131		Citric acid	ES	Stems	$C_6H_8O_7$	192.14	[99]
132		Oxalic acid	ES	Stems	$C_2H_2O_4$	90.04	[99]
133		Fumaric acid	ES	Stems	$C_4H_4O_4$	116.07	[99]
134		Benzoic acid	EE[k], ES	Herbs	$C_7H_6O_2$	122.12	[100]
135		4-*O*-*β*-D-glucoside benzoic acid	ES	Stems	$C_{13}H_{16}O_8$	300.00	[81]
136		*ρ*-hydroxyphenylacetic acid	ES	Stems	$C_8H_8O_3$	152.14	[82]
137		Caffeic acid	ES	Stems	$C_9H_8O_4$	180.15	[82]
138		Chlorogenic acid	ES	Stems	$C_{16}H_{18}O_9$	354.31	[82]
139		Trans-cinnamic acid	ES	Stems	$C_9H_8O_2$	148.15	[82]
140		5-(hydroxy-isopropyl)-cyclohexenecarboxylic acid	ES	Stems	$C_{10}H_{16}O_3$	184.00	[82]
141		Pseudolaroside B	ES	Stems	$C_{14}H_{18}O_9$	330.00	[81]
142		*n*-hexacosane acid	ES	Stems	$C_{26}H_{52}O_2$	396.00	[78]
143		(3*R*)-3-*O*-*β*-D-glucopyranosyl-3-phenylpropanoic acid	ES	Stems	$C_{15}H_{20}O_8$	328.11	[89]
144		4-(2-Eicosyloxycarbonyl-vinyl)-benzoic acid	ES	Herbs	$C_{30}H_{48}O_4$	472.36	[101]
145		4-(2-Docosyloxycarbonyl-vinyl)-benzoic acid	ES	Herbs	$C_{32}H_{52}O_4$	500.39	[101]
146		Ferulic Acid	ES	Roots	$C_{10}H_{10}O_4$	194.19	[6]
147		Iso-ferulic acid	ES	Roots	$C_{10}H_{10}O_4$	194.19	[102]
148		2-hydroxyl-5-methoxybenzoic acid	ES	Roots	$C_8H_8O_4$	168.00	[102]
149		Cinnamic acid	EE	Herbs	$C_9H_8O_2$	148.17	[100]
150		Vanillic acid	EE	Herbs	$C_8H_8O_4$	168.15	[100]
151		*ρ*-hydroxybenzoic acid	EE	Herbs	$C_7H_6O_3$	138.13	[100]
152		*ρ*-coumaric acid	EAL	Herbs	$C_9H_8O_3$	164.16	[68]

Continued

No.	Structural category	Name	Species	PP	CF	FW	References
153		*ρ*-coumaric acid glucoside	ES	Stems	$C_{15}H_{18}O_8$	326.09	[91]
154		Protocatechuic acid	EA	Aerial parts	$C_7H_6O_4$	154.12	[82]
155		Nebrodenside B	EN[l]	Aerial parts	$C_{15}H_{18}O_8$	326.00	[103]
156		Trans-aconitic acid	ES	Stems	$C_6H_6O_6$	174.00	[84]
157		Quinaldic acid	EP[m]	Stems	$C_{10}H_7NO_2$	173.17	[48]

PP: Parts of plants; CF: Chemical formula; FW: Molecular weight; [a] *Ephedra sinica*; [b] *Ephedra aphylla*; [c] *Ephedra intermedia*; [d] *Ephedra transitoria*; [e] *Ephedra pachyclada* ssp. *sinaica*.; [f] *Ephedra foeminea*; [g] *Ephedra foliata*; [h] *Ephedra alata*; [i] *Ephedra campylopoda*; [j] *Ephedra lomatolepis*; [K] *Ephedra equisetina*; [l] *Ephedra nebrodensis*; [m] *Ephedra pachyclada*.

(**130–157**) have been isolated from different *Ephedra* species, whose sources and molecular formulas are shown in Table 2. The representative structural formulas of organic acids are shown in Fig. 2. However, the pharmacological action of organic acids has been rarely reported. To date, organic acids have been investigated worldwide, and further research will promote the development of *Ephedra* organic acids in clinical applications.

Polysaccharides

Since the 1970s, ESP and their pharmacological activities have been recognized and valued. It was reported that *E.* sinica contain approximately 3%–5% polysaccharides [70]. Since ESP has been found to have anti-immunity and anticancer activities, studies on ESP have increased, but the structure of ESP has not been clearly explained. Konno *et al*. [53] extracted glycoproteins with a significant hypoglycemic activity in the aqueous methanol/water extract of *E. distachya* stems. Such glycoproteins include ESP A, B, C, D, and E (**158**, **163**, **168–170**), and the peptide moieties of these glycoproteins are 0.1%. 0.5%, 4.4%, 4.4%, and 3.9%, respectively. The monosaccharide composition and molar ratio of each polysaccharide component have been determined through gas chromatography after hydrolysis. Results show that ESP A is the main polysaccharide, and ESP C and D contain O-acetyl groups, accounting for 1.3% and 3.0%, respectively. Other polysaccharides have also been found in other parts of *Ephedra* herbs. They are water-soluble polysaccharides in *Ephedra* roots; *Ephedra* fruits are rich in reducing sugars (7.21%) and water-soluble sugars (11.58%), exceed 6.16% and 9.65% of that in *Ephedra* stems, respectively [71]. Common polysaccharides, such as starch, pectin, inulin, cellulose, and dextrin, are also found in *Ephedra* herbs [6]. The proportion of each monosaccharide of polysaccharides and the molecular weights, sources, and structural formulas of ESP (**158–170**) are shown in Table 3.

Volatile oils

Ephedra herbs contain approximately 0.15% of volatile oils [67], and their pharmacological activities are usually con-

Table 3 The information of polysaccharides from *Ephedra* plants

No.	Polysaccharides	molecular mass	The monosaccharide Molar ratio									Species	PP	References
			Glu	Gal	Xyl	Man	Ara	Rha	Glu A	Gal A	Tre			
158	ESP-A	1.2×10^6	0.2	1.0	0.7	0.2	0.8	2.4			1.0	ED[a]	Herbs	[53]
159	ESP-A1	5.8×10^4	11.1	11.6	3.2	12.9	61.1					ES[b]	Stems	[104]
160	ESP-A2	2.0×10^6		6.7	20.6		67.7	5.0				ES	Stems	[104]
161	ESP-A3		1.0	22.3	6.8	13.7	7.5	14.0	10.2	3.8		ES	Stems	[105]
162	ESP-A4		1.0	17.3	1.2	1.6	4.1	5.1	3.1	2.2		ES	Stems	[105]
163	ESP-B	1.5×10^6	0.1	1.0	0.9	0.9	0.7	1.0			0.3	ED	Herbs	[53]
164	ESP-B1	6.15×10^3	6.0	1.0		3.0	90.0					ES	Stems	[106]
165	ESP-B2		3.2	13.4	4.7	16.3	21.8	10.3	4.0	26.3		ES	Stems	[106]
166	ESP-B3		4.2	17.8	3.6	8.4	9.7	19.7	4.2	32.4		ES	Stems	[106]
167	ESP-B4	2.0×10^6	1.5	8.3	1.5	1.5	6.8	3.0	2.3	75.2		ES	Stems	[106]
168	ESP-C	1.9×10^4	0.2	1.0		0.3	0.4	0.2				ED	Herbs	[53]
169	ESP-D	6.6×10^3	0.2	1.0		0.1	1.0	0.5	1.0	2.1		ED	Herbs	[53]
170	ESP-E	3.4×10^4	0.7	1.0		0.3	0.4	0.4				ED	Herbs	[53]

Glu:Glucose; Gal: Galactose; Xyl: Xylose; Man: Mannose; Ara: Arabinose; Rha: Rhamnose; Tre: Trehalose; ESP: *Ephedra* Polysaccharides; PP: Parts of plants; [a] *Ephedra distachya*; [b] *Ephedra sinica*.

sidered to be antipyretic, sudoriferous, and anti-inflammatory. Many scholars studied volatile oils in *Ephedra* herbs, and more than 200 kinds of volatile oils have been extracted from *Ephedra* herbs mainly include alcohols and terpenes [72,73]. However, their contents vary according to different reports, and they may be related to environmental factors, such as different origins, soil properties, harvesting periods, and growth periods. We summarize 31 high-content volatile oils in *Ephedra* herb and find that roots and stems contain volatile oils, but the content and types of volatile oils in stems are higher than those in roots. The chemical structures of important volatile oils (**171**–**201**) are illustrated in Fig. 3. The sources and relative contents of common volatile oils are shown in Table 4.

Other compounds

Other uncommon compounds with important biological activities have been found in different parts of *Ephedra* species. They are eight phenols, three naphthalenes [74], two amides [75], two ethers [76, 77], nine esters [78], seven terpenes [79, 80], one urea [49], three nucleic acids [81], two anthraquinones [82], and three lignins [68, 75]. Abundant amino acids and their biological functions have been reported in *Ephedra* roots, stems, seeds, and fruits. Four cyclopropane amino acids were isolated from *Ephedra* herbs [83] besides widely known alanine

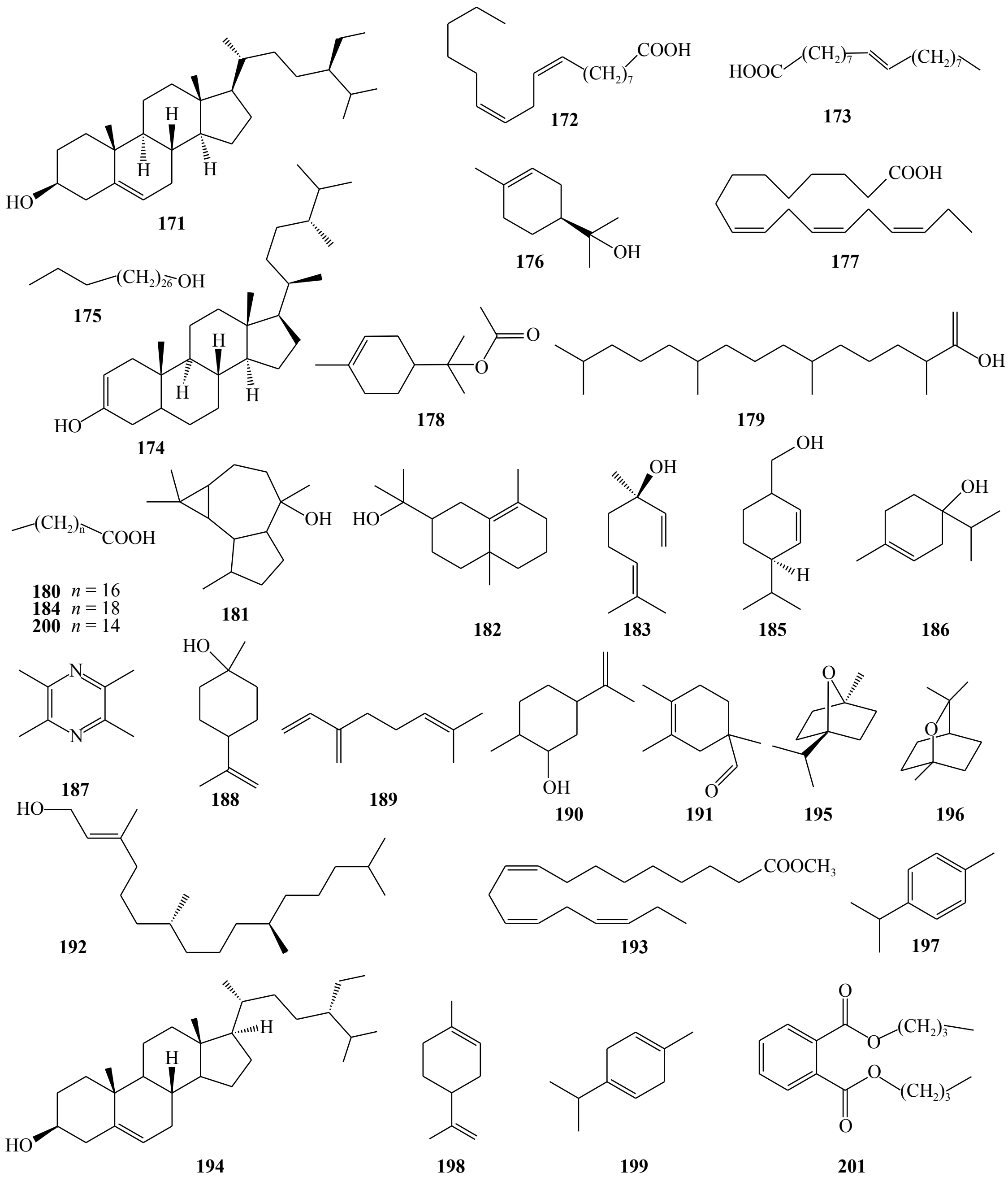


Fig. 3 The chemical structures of volatile oils from *Ephedra* plants

Table 4 The information of volatile oils from *Ephedra* plants

No.	Name	Species	PP	RC	References
171	*β*-sitosterol	ES[a]	Roots	28.55	[73]
172	9*Z*, 12*Z*-octadecadienoic acid	ES	Roots	17.71	[73]
173	9-*E*-octadecenoic acid	ES	Roots	7.99	[73]
174	Ergost-5-en-3*β*-ol	ES	Roots	7.51	[73]
175	Nonacosanol	ES	Roots	5.07	[73]
176	L-*α*-terpineol	ES	Stems	31.64	[72]
177	Linolenic acid	ES	Stems	21.29	[73]
178	Terpineol acetate	ES	Stems	17.05	[107]
179	3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol	ES	Stems	9.72	[73]
180	Stearic acid	ES	Stems	4.42	[73]
181	Globulol	ES	Stems	3.68	[107]
182	*γ*-eudesmol	ES	Stems	3.43	[72]
183	Linalool	ES	Stems	3.26	[72]
184	Eicosanoic acid	ES	Stems	3.02	[73]
185	Cis-2-*ρ*-menthen-7-ol	ES	Stems	2.19	[72]
186	Terpinen-4-ol	ES	Stems	1.90	[72]
187	Tetramethylpyrazine	ES	Stems	1.00	[72]
188	*β*-terpineol	ES	Stems	—	[22]
189	Myrcene	ES	Stems	—	[22]
190	Dihydrocarveol	ES	Stems	—	[22]
191	1, 3, 4-trimethyl-3-cyclohexene-1-carboxaldehyde	ES	Stems	—	[22]
192	Trans-phytol	EC[b]	Stems	39.17	[75]
193	Linolenic acid methyl ester	EC	Stems	6.33	[75]
194	*γ*-sitosterol	EC	Stems	4.97	[75]
195	1, 4-cineole	EI[c]	Stems	12.80	[72]
196	1, 8-cineole	EI	Stems	9.90	[72]
197	*ρ*-cymene	EI	Stems	9.70	[72]
198	Limonene	EI	Stems	4.90	[72]
199	*γ*-terpinene	EI	Stems	4.29	[72]
200	Hexadecanoic acid	EE[d]	Stems	26.22	[72]
201	Dibutyl phthalate	EE	Stems	10.48	[72]

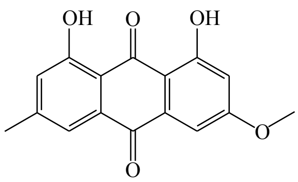
PP: Parts of plants; RC: Relative content; [a] *Ephedra sinica*; [b] *Ephedra campylopoda*; [c] *Ephedra intermedia*; [d] *Ephedra equisetina*.

and glutamic acid [84]. The structural formulas of some important compounds (**202**–**247**) are presented in Fig. 4. The sources, structural formulas, and molecular weights of all these compounds are listed in Table 5.

Conclusion and Prospect

In conclusion, *Ephedra* herb has played an indispensable role in treating various diseases for a long time in history. Additionally, the studies about chemical composition and pharmacological effects of *Ephedra* herb are increasing year by year, which can provide bran-new insight for the understanding of *Ephedra* herbs composition and its clinical applications. *Ephedra* herbs have been widely used as pharmaceuticals and dietary supplements. In the future, this ancient medicinal plant will continue to play a remarkable role in terms of pharmacological and economic value.

Although alkaloids in *Ephedra* herbs show diverse pharmacological effects, its adverse reactions should not be underestimated. The pharmacological effects of multiple components in *Ephedra* herbs should be studied in depth. In the future, efforts should be devoted to studying the following aspects: some scholars predict that immunosuppressants from Chinese herbal medicines will be widely explored. ESP as an immune regulator has a unique advantage. Its low side effect has been approved by international medical communities. Thus, ESP of *Ephedra* herb should be further explored. Second, the volatile oils of *Ephedra* herb are often overlooked, but their medicinal value should be investigated. Third, the research and application of *Ephedra* roots and fruits are relatively weak, but they are often used in folk food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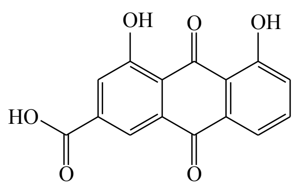
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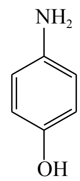
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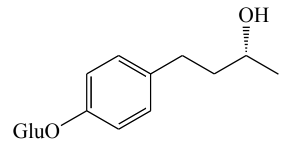
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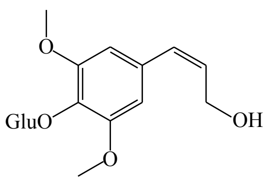
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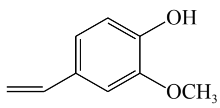
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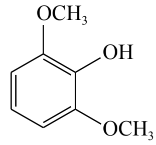
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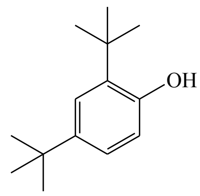
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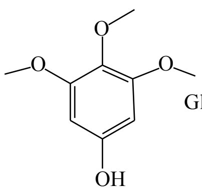
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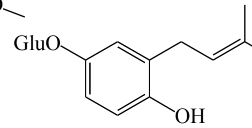
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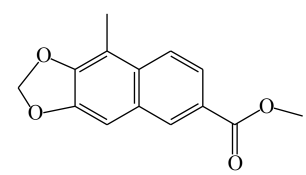
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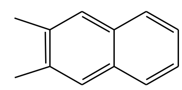
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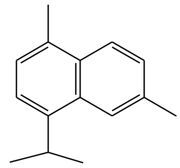
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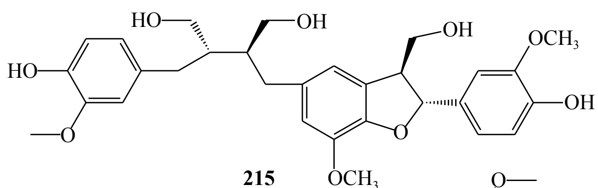
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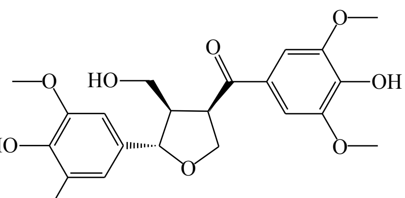
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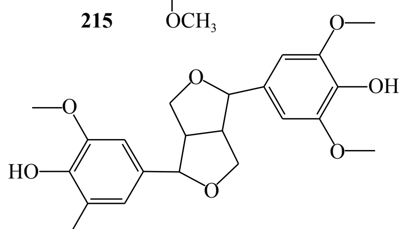
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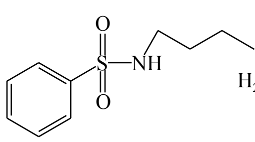
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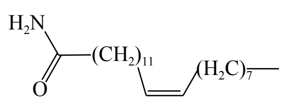
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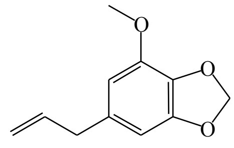
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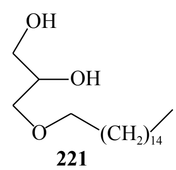
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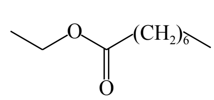
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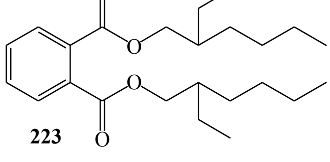
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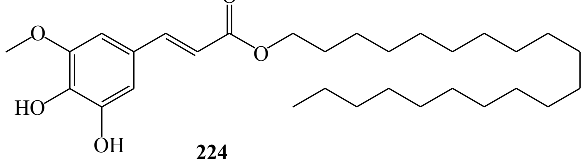
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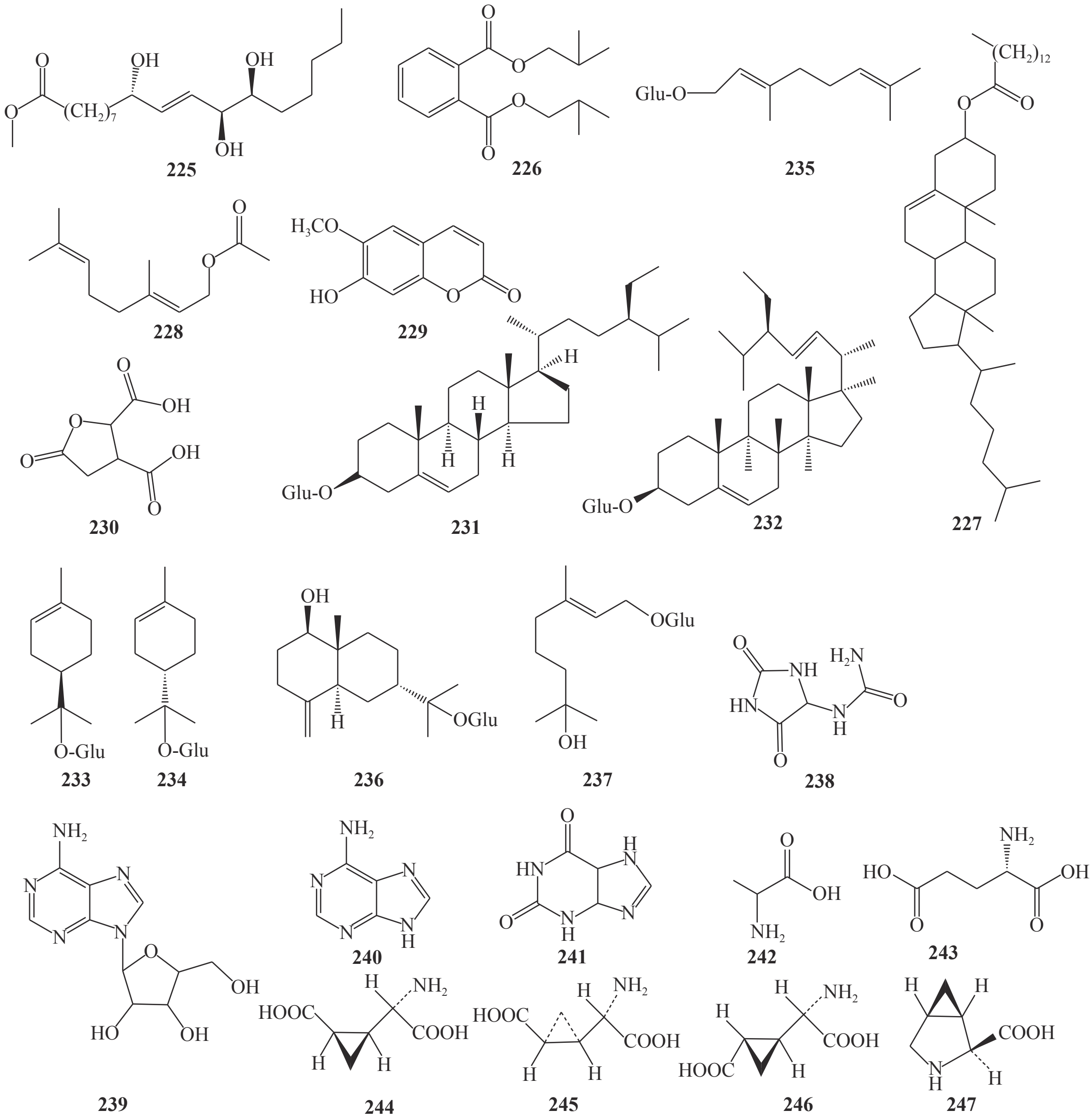

Fig. 4 The chemical structures of trace or rare compounds from *Ephedra* plants

Table 5 The information of uncommon compounds from *Ephedra* plants

No.	Structural category	Name	Species	PP	CF	FW	References
202	Anthraquinones	Physcion	ES[a]	Stems	$C_{16}H_{12}O_5$	284.27	[82]
203		Rhein	ES	Stems	$C_{15}H_8O_6$	284.22	[82]
204	Phenols	*p*-aminophenol	ES	Stems	C_6H_7NO	109.13	[82]
205		Rhododendrol-4′-*O*-*β*-D-glucopyranoside	ES	Stems	$C_{16}H_{24}O_7$	328.00	[81]
206		Cis-syringin	ES	Stems	$C_{17}H_{24}O_9$	372.00	[81]
207		Vinylguaiacol	EC[b]	Stems	$C_9H_{10}O_2$	150.17	[75]
208		Syringol	EC	Stems	$C_8H_{10}O_3$	154.16	[75]
209		Di-tert-butylphenol	EC	Stems	$C_{14}H_{22}O$	206.32	[75]
210		Antiarol	EC	Stems	$C_9H_{12}O_4$	184.20	[75]
211		Nebrodenside A	EN[c]	Aerial parts	$C_{17}H_{24}O_7$	340.00	[103]

Continued

No.	Structural category	Name	Species	PP	CF	FW	References
212	Naphthalenes	1-methyl-2, 3-methylenedioxy-6-naphthalenecarboxylic acidmethyl ester	ES	Stems	$C_{14}H_{12}O_4$	244.00	[74]
213		2, 3-dimethylnaphthalene	ES	Roots	$C_{12}H_{12}$	156.00	[76]
214		4-isopropyl-1, 6-dimethylnaphthalene	ES	Roots	$C_{15}H_{18}$	198.00	[76]
215	Lignins	Sesquipinsapol B	ES	Roots	$C_{30}H_{36}O_9$	540.00	[102]
216		Ciwujiatone	ES	Stems	$C_{22}H_{26}O_9$	434.44	[78]
217		DL-syringaresinol	EAL[d]	Herbs	$C_{22}H_{26}O_8$	418.44	[68]
218	Amides	N-butylbenzenesulfonamide	EC	Stems	$C_{10}H_{15}NO_2S$	213.30	[75]
219		Erucylamide	ES	Herbs	$C_{22}H_{43}NO$	337.00	[76]
220	Ethers	Myristicin	ES	Roots	$C_{11}H_{12}O_3$	192.00	[76]
221		3-(hexadecyloxy)propane-1, 2-diol	ES	Roots	$C_{19}H_{40}O_3$	316.00	[77]
222	Esters	Ethyl caprylate	ES	Roots	$C_{10}H_{20}O_2$	172.00	[80]
223		Bis(2-ethylhexyl)phthalate	ES	Roots	$C_{24}H_{38}O_4$	390.00	[77]
224		(*E*)-eicosyl-4, 5-dihydroxy-3-methoxy cinnamate	ES	Roots	$C_{30}H_{50}O_5$	490.37	[77]
225		(9*S*, 10*E*, 12*S*, 13*S*)-9, 12, 13-trihydroxy-10-octadecenoic acid methyl ester	ES	Roots	$C_{19}H_{36}O_5$	344.00	[102]
226		Phthalic acid-diisobutyl ester	ES	Roots	$C_{16}H_{22}O_4$	278.00	[76]
227		Cholestane-5-ene-3*β*-tetradecanoate	ES	Stems	$C_{41}H_{72}O_2$	596.00	[78]
228		Geranyl acetate	ES	Herbs	$C_{12}H_{20}O_2$	196.00	[76]
229		Scopoletin	ES	Stems	$C_{10}H_8O_4$	192.17	[79]
230		Isocitric lactone	ES	Stems	$C_6H_6O_6$	174.11	[84]
231	Terpenoids	Daucosterol	ES	Roots	$C_{35}H_{60}O_6$	576.85	[102]
232		Stigmasterol-3-*O*-*β*-D-glucopyranoside	ES	Roots	$C_{35}H_{58}O_6$	574.00	[80]
233		(−)-*α*-terpineol-8-*O*-*β*-D-glucopyranoside	ES	Roots	$C_{16}H_{28}O_6$	316.00	[102]
234		(+)-*α*-terpineol-8-*O*-*β*-D-glucopyranoside	ES	Roots	$C_{16}H_{28}O_6$	316.00	[102]
235		Geranyl-*β*-D-glucopyranoside	ES	Roots	$C_{16}H_{28}O_6$	316.00	[102]
236		Epheganoside	ES	Stems	$C_{21}H_{36}O_7$	400.00	[79]
237		(*E*)-7-hydroxy-3, 7-dimethyloct-2-en-1-yl-*β*-*d*-*O*-glucopyranoside	ES	Stems	$C_{16}H_{30}O_7$	334.00	[79]
238	Ureas	Allantoin	ES	Stems	$C_4H_6N_4O_3$	158.00	[49]
239	Nucleic acids	Adenosine	ES	Roots	$C_{10}H_{13}N_5O_4$	267.24	[81]
240		Adenine	ES	Stems	$C_5H_5N_5$	135.00	[49]
241		Xanthine	ES	Roots	$C_5H_4N_4O_2$	152.11	[81]
242	Amino acids	Alanine	ES	Stems	$C_3H_7NO_2$	89.00	[84]
243		Glutamic acid	ES	Roots	$C_5H_9NO_4$	147.00	[84]
244		(2*S*, 3*S*, 4*R*)-2-(carboxycyclopropyl)glycine	EFOE[e], EALT[f]	Stems	$C_6H_9NO_4$	159.00	[83]
245		(2*S*, 3*R*, 4*S*)-2-(carboxycyclopropyl)glycine	EFOE, EALT	Stems	$C_6H_9NO_4$	159.00	[83]
246		(2*S*, 3*S*, 4*S*)-2-(carboxycyclopropyl)glycine	EALT	Seeds	$C_6H_9NO_4$	159.00	[83]
247		Cis-3, 4-methanoproline	EFOL[g], EFOE	Seeds	$C_6H_9NO_2$	127.00	[83]

PP: Parts of plants; CF: Chemical formula; FW: Molecular Weight; [a] *Ephedra* sinica; [b] *Ephedra campylopoda*; [c] *Ephedra nebrodensis*; [d] *Ephedra alata*; [e] *Ephedra foeminea*; [f] *Ephedra altissima*; [g] *Ephedra foliate*.

or healthcare, and their medicinal value should be maximized. Strengthening research on the application of whole *Ephedra* herb will contribute to the economical utilization of *Ephedra* herb. Fourth, many species or varieties of *Ephedra* herbs have not been widely studied and used, and the medicinal value of each species should be elucidated. Fifth, the combined use of *Ephedra* herbs and other botanical drugs can address new challenges and threats, and this aspect should also be investigated. Finally, new techniques should be adopted to further promote and understand the applications of *Ephedra* herbs.

Additionally, most *Ephedra* herbs have been collected from wild plants, and excessive harvesting has led to the shortage of wild resources and ecological destruction. The management, orderly collection, artificial breeding, and cultivation of *Ephedra* herb should be strengthened to establish an *Ephedra* planting base that meets the standard of good agriculture practice. Thus, our future goal is to adopt modern technology for producing high-quality and high-yielding *Ephedra* herbs, protecting wild *Ephedra* resources, promoting their orderly and sustainable utilization, and providing benefits to humans.

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