

Ethnobotanical Uses and Pharmacological Activities of Moroccan *Ephedra* Species

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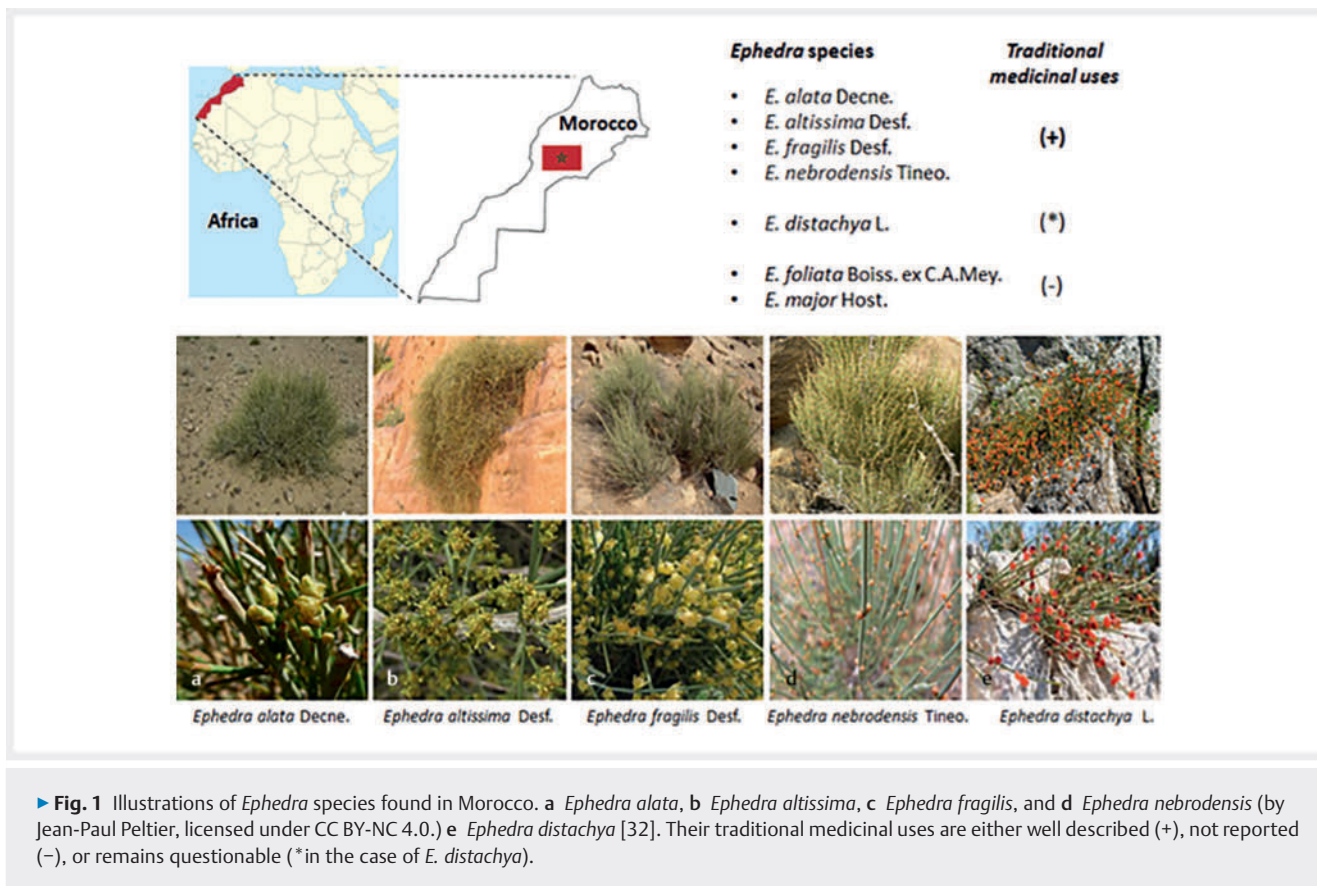
ABSTRACT

Ephedra species are among the most popular herbs used in traditional medicine for a long time. The ancient Chinese medical book “Treatise on Febrile Diseases” refers to the classic traditional Chinese medicine prescription Ge Gen decoction, which consists of seven herbs, including an *Ephedra* species. *Ephedra* species are utilized all over the world to treat symptoms of the common cold and coughs, and to combat major human diseases, such as asthma, cancers, diabetes, cardiovascular and digestive disorders, and microbial infections. This study aimed at identifying specific *Ephedra* species used traditionally in Morocco for therapeutic purposes. The plant parts, their preparation process, and the treated pathologies were identified and analyzed. The results revealed five ethnobotanically important species of *Ephedra*: *Ephedra alata* Decne, *Ephedra altissima* Desf., *Ephedra distachya* L., *Ephedra fragilis* Desf., and *Ephedra nebrodensis* Tineo. These species are used traditionally in Morocco for treating people with diabetes, cancer, rheumatism, cold and asthma, hypertension, influenza virus infection, and respiratory ailments. In addition, they are occasionally used as calefacient agents, to regulate weight, or for capillary care. Few studies have underlined the antibacterial and antioxidant activities of some of these Moroccan *Ephedra* species, but little information is available regarding the natural products at the origin of the bioactivities. Further phytochemical investigations and clinical data are encouraged to better support the use of these plants.

Introduction

Ephedra plants are among the oldest and most popular herbs used in traditional medicine in China and Japan [1–3]. *Ephedrae herba* has long been used as both medicine and food [4,5]. It stands as an efficient anti-stroke herbal medicine [6]. Its use as a folk phyto-medicine is mentioned in ancient medical books and traditional prescriptions [3]. For example, the ancient Chinese medical book

“Treatise on Febrile Diseases” refers to the classic traditional Chinese medicine prescription Ge Gen decoction, which consists of seven herbs, including an *Ephedra* species [7], and a Latin textbook from the roman naturalist Pliny the Elder (Gaius Plinius Secundus, AD 23–79) underlined the use of *Ephedra* as follows: “it is given from black austere wine, crushed, for coughs, sighs, convulsions, and drinking” [8]. For decades, *Ephedra* species have provided herbal remedies to treat human diseases [9, 10]. These medicinal



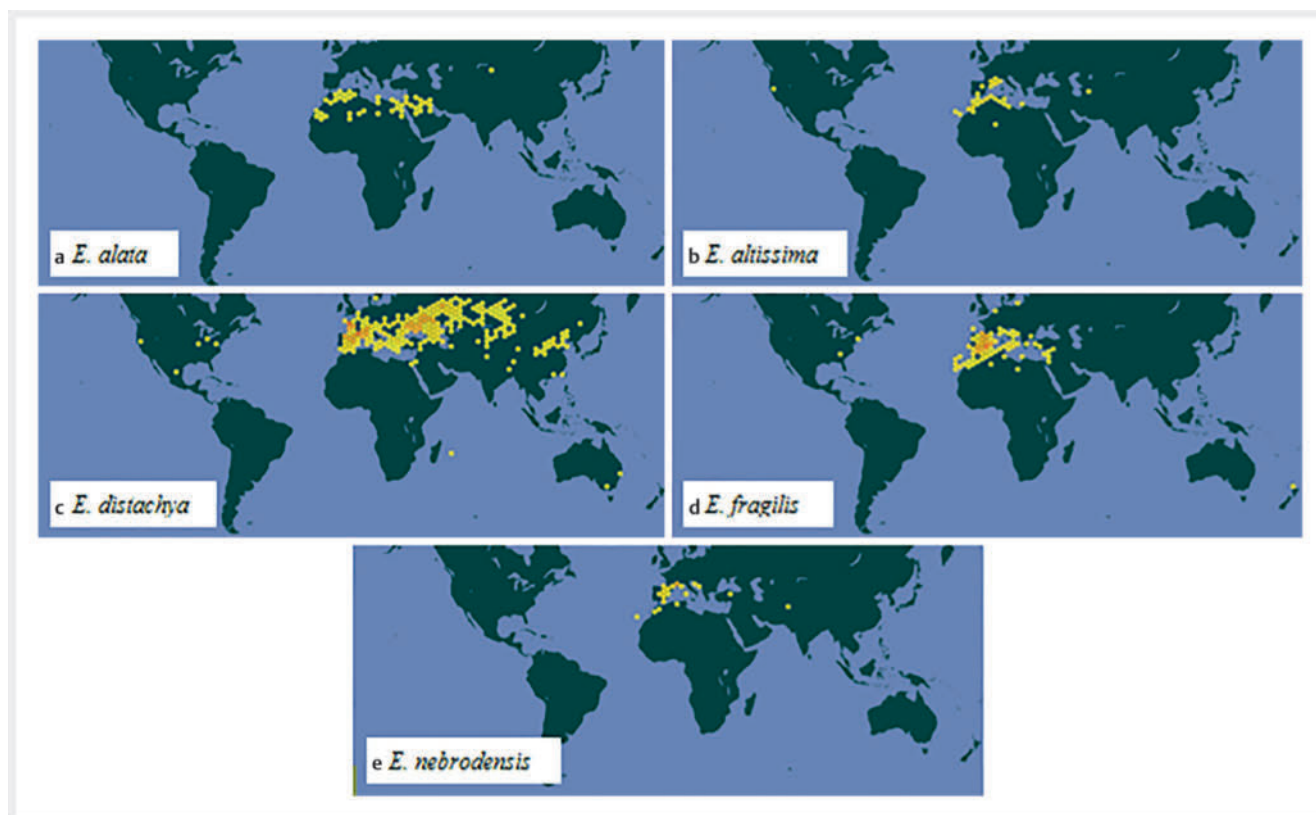
plants, largely distributed in arid and semiarid regions of the world, also carry ecological and economic values [11, 12].

Over 60 *Ephedra* plants have been identified [4, 11]. The POWO database has listed 167 species, including 78 with accepted names (https://powo.science.kew.org/results?f=species_f%2Caccepted_names&q=Ephedra). *Ephedra* species can be found in Europe, southern and eastern Asia (notably in China and Japan), North America (southwestern United States and northern Mexico), the western part of South America, and in Africa, from North Africa to the horn of Africa. *Ephedra* species grow in desert, arid, and semiarid conditions, most often on dry, rocky, or sandy soil. They are often considered desert shrubs, but some species can be found in riverbeds and grasslands [10, 13].

In traditional medicine, the uses of *Ephedra* species are extremely diversified. They are utilized to treat respiratory affections, such as cough, symptoms of the common cold and asthma, or as a deobstruent or emollient. These plants are also used to treat disorders of the cardiovascular and digestive systems, ailments of the urinary tract, cancers, diabetes, as well as bacterial, viral, and fungal infections [14, 15]. Other studies mention the use of *Ephedra* species for the treatment of edema, fever, and allergies [1, 2, 16, 17]. *Ephedra* extracts are also considered as dietary supplements, notably for weight loss [18, 19]. However, it is important to mention that despite the recognized benefits of *Ephedra* herbs on human health, adverse effects have occasionally been recorded, such as excitation, agitation, palpitation, dysuria, arrhythmia, elevated blood pressure, dizziness, and insomnia [2, 20, 21].

These undesirable reactions were generally related to the presence of ephedrine-type alkaloids [21, 22]. The alkaloid ephedrine, often present in *Ephedra* herb extracts, mediates sustained excitatory effects via activation of the α -2a adrenoceptor [23]. Over the past 10 years, the development of an ephedrine alkaloid-free *Ephedra* herb extract has been recommended for safer use by humans, with reduced side effects [21, 22, 24, 25]. Ephedrine-free *Ephedra* herb extract and derived products can be used to treat various diseases, including COVID-19, for example [2, 26].

Ephedra species are used as medicinal plants in African and Mediterranean countries. For example, the species *Ephedra foeminea* Forssk is a traditional medicinal plant in the Eastern Mediterranean region [27]. In Lebanon, this plant offers a popular remedy to treat inflammation and bacterial infections [28]. The species *Ephedra nebrodensis* Tineo growing in Algeria is largely used to combat inflammatory and oxidative damage [29, 30]. The two species *Ephedra alata* and *Ephedra altissima* growing in Tunisian arid zones are used traditionally to treat chills, coughs, fever, and bronchial asthma [31]. In the present work, we have identified the *Ephedra* species used specifically in Morocco (► Fig. 1). We inventoried their traditional medicinal uses by local populations and the main bioactive products and associated pharmacological activities have been analyzed. The aim of this analysis is to highlight the use of *Ephedra* species in Morocco, to encourage further studies on the plant's pharmacological activities, and to try to provide a scientific rationale for their medicinal usage.



► **Fig. 2** Distribution of the five species of *Ephedra* around the world (maps defined from the Global Biodiversity Information Facility [gbif.org]) [33, 42, 47, 54, 57].

Results

Ephedra species around the world

Ephedra species are dispersed in arid and semiarid areas of Asia, Europe, Northern Africa, southern North America, and South America [11]. The five species discussed in this paper are mainly present in North Africa and Eurasia (► **Fig. 2**). *E. alata* is located in North Africa and West Asia (► **Fig. 2 a**) [33], and was cited among the flora of Morocco [34–36], Algeria [37], Tunisia [38, 39], and Palestine [40]. *E. altissima* is limited to North Africa and the south of Europe [41] (► **Fig. 2 b**) [42], including countries such as Austria (botanical garden) [43] and Morocco [44–46]. *Ephedra distachya* is the most abundant of these species and belongs to the extreme north of Africa and Eurasia (► **Fig. 2 c**) [47]. Samples from China [48], Morocco [49, 50], Greece [51], Spain [52], Ukraine [53], and Austria [43] have been reported. *Ephedra fragilis* is distributed in North Africa and Europe (► **Fig. 2 d**) [54] as well as in Morocco [44, 55] and Austria [43]. Finally, *Ephedra nebrodensis*, which has the lowest distribution, can be found in North Africa [56], Europe (► **Fig. 2 e**) [57], including Italy [58, 59] and Spain [52], Morocco [60], and Algeria [61]. Here, we will focus on Moroccan *Ephedra* species.

Ephedra species found in Morocco and their medicinal uses

Several ethnobotanical surveys and floristic studies have been performed in different regions of Morocco to take inventory of the flora species of the country. For example, recent studies refer to the medicinal plants used traditionally in the Safi and Sefrou provinces [62, 63] or the Ksar Elkebir [64] and Tafilalet regions [65]. Toxic plants found in northeastern Morocco have been inventoried as well [20]. Other studies cover different local areas or they are concerned with specific pathology or disorders, such as the Moroccan plants used to treat cancers [14, 66], skin affections [67], kidney diseases [68], or cardiovascular diseases [69]. Some Moroccan plants have been largely studied, such as the endemic argan [*Argania spinosa* (L.) Skeels], which is well known for its famous oil extracted from argan seeds [70]. However, there is no study focused on Moroccan *Ephedra* species and their medicinal uses. We performed this specific analysis.

We identified five medicinal *Ephedra* species present in Morocco, namely, *E. alata*, *E. altissima*, *E. distachya*, *E. fragilis*, and *E. nebrodensis* (► **Fig. 1** and **Table 1**). They are essentially located in the southern part of the country, but also in the Middle and High Atlas Mountains. The ethnobotanical information on Moroccan *Ephedra* is limited, probably because the density of the population is low in south Morocco and because of the aridity of the region. *Ephedra* species are not abundant compared to other plants. For example, Abouri and coworkers identified 163 plant species re-

► **Table 1** *Ephedra* species of Morocco and their locations.

<i>Ephedra</i> species	Location in Morocco	Reference
<i>Ephedra alata</i>	Laâyoune Sakia El Hamra region	[35]
	Tarfaya Province	[36]
	Tata Province	[34]
<i>Ephedra altissima</i>	Atlas Mountains, Imouzzer region	[44–46]
<i>Ephedra fragilis</i>	Southern Morocco	[71, 72]
	Oulad Teima, Taroudant Souss-Massa region	[44, 55]
<i>Ephedra nebrodensis</i>	Central Middle Atlas	[15]
	High Atlas	[60]
	Tichoukt Mountain, Middle Atlas	[56]
<i>Ephedra distachya</i>	Southern Morocco	[49, 50]

presenting 134 genera in the Tata province (south-eastern Morocco) but only one *Ephedra* species, *E. alata* Decne. (known locally as Tamatrt), which is used traditionally mainly to treat colds and respiratory ailments. Ephedraceae appeared to be rare in this part of the country, in contrast to Lamiaceae and Asteraceae, which are much more abundant [34]. The situation is a little more favorable in the Middle and High Atlas Range, with a more frequent presence of *Ephedra* species, such as *E. nebrodensis* Guss. found on the rocky ecosystem (from 2200 meters) [56].

The five *Ephedra* species present in Morocco are used traditionally to treat different diseases (► **Table 2**). Four of them are well referenced, but there is no published information on the local (Moroccan) use of *E. distachya* L. to treat human diseases. However, this plant is cited as a medicinal plant in other countries, owing to its content of catechins and other polyphenolic compounds with antioxidant and anti-inflammatory properties [73, 74]. We choose to maintain this species in our analysis because the presence of the plant in Morocco has been clearly mentioned [49, 50] and practitioners have cited this species also. Two other *Ephedra* species are present in Morocco, *Ephedra foliata* Boiss. ex C. A. Mey. and *Ephedra major* Host, but we did not identify any study pertaining to the traditional medicinal use of these species. For this reason, we did not consider them in our study (► **Fig. 1**). The most frequently cited species is *E. alata* Decne. followed by *E. altissima* Desf., *E. fragilis* Desf., and then *E. nebrodensis* Tineo. This latter species can be commonly found in other Mediterranean countries such as Algeria and Italy [29, 58] and more rarely in other parts of the world, such as Pakistan [75]. Altogether, they are used locally to treat a variety of human diseases, such as asthma, rheumatism, hypertension, diabetes, cancer, and other pathologies or conditions (► **Table 2**). The aerial parts of the plants are used to make decoctions from the leaves or stems. *E. alata* is the most frequently used *Ephedra* species in the form of decoction (powdered branches) or infusion (leaves) and the preparations are used orally

or inhaled to treat respiratory ailments. There is also a mention of massage using a decoction to treat rheumatoid arthritis [34]. Decoctions made from the aerial parts of *E. altissima* are used to treat diabetes and cancer. However, this product should be used with care because it can induce neurological damages, notably dizziness or vertigo [20]. *E. alata* is perhaps a safer species, with no major toxicity reported, in particular, no hallucinogenic effect when a plant decoction is used for oral treatment of diabetes in the Zagora region of Morocco [76]. However, caution is required because *Ephedra* preparations containing the alkaloid ephedrine may cause hypotension and spontaneous abortion in pregnant women [77].

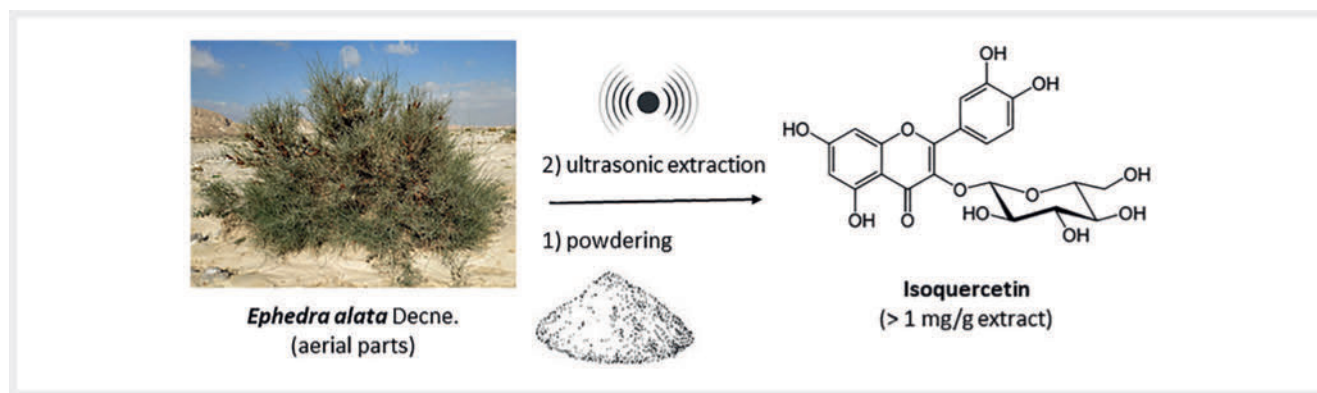
Pharmacological activities of *Ephedra* extracts and associated bioactive products

Experimental studies performed with plant extracts made from Moroccan *Ephedra* are rare, but there are a few useful reports (► **Table 3**) that can be completed with studies using the same species collected from other countries. Thereafter, the plant extract activities are discussed in turn.

Ephedra alata Decne

The dried aerial parts of a sample of *E. alata* collected from the Laâyoune Sakia El Hamra region (Morocco) have been used to prepare a plant extract via an ultrasound-assisted extraction process with the objective of optimizing the yield of the main active ingredient from the extract, the flavonoid glycoside isoquercetin [35]. The process afforded more than 1 mg of isoquercetin per gram of extract. The isoquercetin-enriched extract was shown to display higher antioxidant and enzymatic effects than a classical extract obtained with a conventional Soxhlet extraction. The enriched extract showed a higher inhibitory efficiency against different enzymes, such as elastase and collagenase implicated in skin aging, tyrosinase involved in hyperpigmentation, α -amylase playing a role in diabetes, hyaluronidase involved in inflammation processes, and cholinesterase implicated in some neurodegenerative disorders. The content of isoquercetin was largely enhanced and the associated bioactivities reinforced [35]. Isoquercetin (quercetin 3-glucoside, also called isoquercitrin) (► **Fig. 3**) is a major constituent of *E. alata* and a well-known flavonoid found in a variety of plants, with anti-neuroinflammatory and anticancer activities [84–87]. Recently, this compound has been characterized as a promising molecule for the treatment of osteoporosis [88].

E. alata is one of the medicinal plants used to treat cancer in Morocco [14, 66] and in other countries, such as Algeria and Palestine (East Jerusalem) [89, 90]. Methanolic or ethanolic extracts made from the plant have revealed marked inhibitory effects on the proliferation of breast cancer cell lines *in vitro*. The activity has been associated with the presence of diverse flavonoids, phenolic acids, and proanthocyanidins [37, 91–93]. A recent study evidenced the induction of tumor cell apoptosis in a p53-dependent manner by an ethanolic extract of *E. alata* (with a specimen from Algeria) [94]. Isoquercetin contributes to the anticancer effects in conjunction with other glycosylated flavonoids, such as luteolin-7-O-glucuronide and myricetin-3-rhamnoside, which have been characterized in a sample of a wild *E. alata* plant [40]. Other bioactivities have been characterized with *E. alata* extracts, includ-



► **Fig. 3** *E. alata* with the extraction and purification process developed to efficiently extract isoquercetin [35] (photo of the plant from POWO [<https://powo.science.kew.org>]).

► **Table 2** Medicinal traditional uses of *Ephedra* species from Morocco.

Ephedra species	Local vernacular name	Therapeutic traditional uses	Part of the plant used	Method of preparation	Moroccan study area	References
<i>Ephedra nebrodensis</i>	Timitrte	Antidiabetic	Leaves	Leaf decoction associated with <i>Apium graveolens</i> and <i>Petroselinum sativum</i>	Central Middle Atlas region	[15]
<i>Ephedra alata</i>	Daghmous Elaalnda	Cancer	Leaves, stems	Decoction (oral administration)	Greater Casablanca	[14]
	Chdida	Rheumatism, colds	Leaves, stems	Oral powder	Tarfaya Province	[36]
	Andla	Cancer	Leaves	Infusion, powder for internal or external uses		[66]
	Amater	Asthma, arthritis/rheumatoid	Stems	Decoction (oral/ointment)		[78]
	Tamatrt	To gain weight, caloric, diabetes, asthma, hypertension, colds, influenza, respiratory ailments, rheumatoid arthritis	Leaves, branches	Oral, inhalation, massage	Tata Province	[34]
<i>Ephedra altissima</i>		Diabetes	Leaves	Decoction powder/oral	Zagora	[76]
	Tougel argan	Diabetes	Stems, leaves, and whole plant	Decoction/oral	Chtouka Ait Baha and Tiznit (Western Anti-Atlas)	[79]
	Laâlenda	Abortion	Stems			[80]
<i>Ephedra fragilis</i>	Laâlenda	Cancer	Aerial part	Internal uses	Northeastern Morocco	[20]
	Azrm Amater	Hair care and diabetes	Aerial part Leafy stems	Decoction	Northeastern Morocco	[81]
	Amater	Diabetes	Leafy stems	Decoction/oral	Taroudant Province	[82]

► **Table 3** Studies about *Ephedra* species from Morocco.

Ephedra species	Plant part and preparation used	Main activity studied	Results	References
<i>Ephedra alata</i>	Aerial parts, ethanol extract	Enzyme inhibitory and antioxidant activities; extraction of isoquercetin	Antioxidant and inhibitory activities against diverse enzymes (acetyl- and butyryl-cholinesterase, α -amylase, elastase, hyaluronidase). Optimization of the extraction process for isoquercetin (recovery: 1034 $\mu\text{g/g}$ of extract using optimized parameters: EtOH concentration, liquid-solid ratio, extraction time, extraction temperature, and ultrasonic power).	[35]
<i>Ephedra altissima</i>	Roots, methanolic extract	Anti-staphylococcal activity	Antibacterial activities of the extract, notably against <i>Staphylococcus epidermidis</i> and two strains of <i>Staphylococcus aureus</i> .	[45]
	Roots, methanolic extract	Antileishmanial activity	The alcoholic extract was found active against <i>Leishmania infantum</i> ($\text{IC}_{50} = 490.8 \mu\text{g/mL}$).	[46]
<i>Ephedra fragilis</i>	Aerial parts, several organic extracts	Antioxidant, anti-glycation activities; chemical composition	Marked antioxidant activity of the ethyl acetate fraction. Identification of rutin, quercetin, caffeic, ferulic acid, gallic acid, and vanillic acid.	[55]
	Aerial parts, ethyl acetate extract	Cytoprotective effect	Protection of <i>Tetrahymena pyriformis</i> cells from oxidative stress induced by hydrogen peroxide.	[83]

ing antioxidant and anti-inflammatory effects [16], notably associated with the presence of glycosylated flavonoids such as isorhamnetin-3-*O*-rutinoside, isoschaftoside, and kaempferol-3-*O*-rhamnoside [95]. There is also mention of antidiabetic and antibacterial activities with this plant [96–99]. Aqueous extracts of *E. alata* contain diverse flavonoids but also alkaloids, phenolic compounds, and steroids useful to improve wound healing [100].

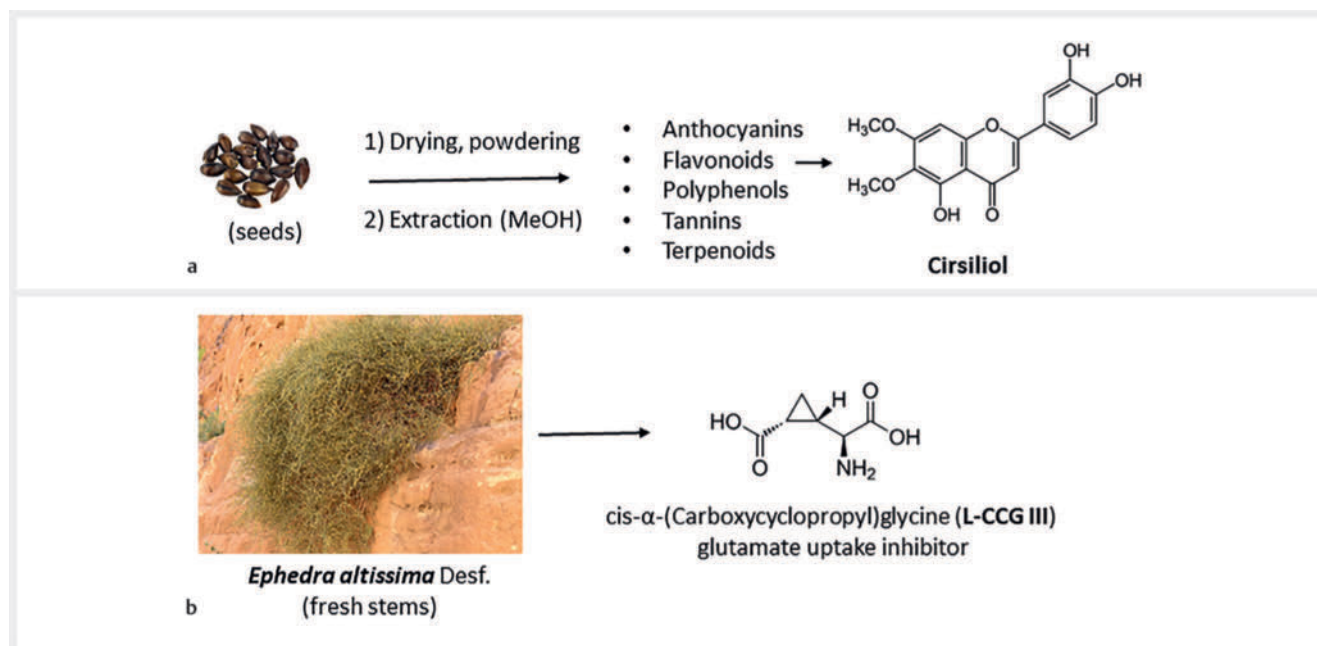
Ephedra altissima Desf.

This *Ephedra* species is native to the north of Africa (Morocco, Algeria, Tunisia, Libya, and Mauritania), the Canary Islands, and Chad. A plant sample collected in the Atlas Mountains in the Imouzzer region of Morocco has been used to prepare both aqueous and methanolic extracts of *E. altissima* that were then tested for their antibacterial activities. The aqueous extracts were found inactive, whereas methanolic extracts made from the plant roots revealed a modest activity against *Staphylococcus aureus* [strain ATCC 29213, which is a classical methicillin-resistant (MRSA) strain]. The antibacterial activity was noticeable but weak compared to that measured with other Moroccan plants, such as *Berberis hispanica*, for example [45]. The authors also evaluated the capacity of the plant extracts to inhibit the growth of the promastigote forms of *Leishmania* parasites, responsible for cutaneous leishmaniasis. The extract from *E. altissima* revealed a modest activity against *Leishmania infantum* ($\text{IC}_{50} = 490.8 \mu\text{g/mL}$) [46]. These are the only studies performed with samples of *E. altissima* collected in Morocco.

Other studies have evaluated the bioactivities of *E. altissima* extracts but with plant specimens collected from other countries. In particular, a recent work evidenced the antibacterial effects of an ethyl acetate extract from an Algerian sample of the plant (collected in Bouhmama County). It revealed inhibitory activities against the two enzymes, α -amylase ($\text{IC}_{50} = 8.07 \mu\text{g/mL}$) and pancreatic lipase ($\text{IC}_{50} = 289.1 \mu\text{g/mL}$), coupled with an anti-inflammatory effect ($\text{IC}_{50} = 126.4 \mu\text{g/mL}$), possibly explaining the activ-

ity of the plant against type 2 diabetes [101]. The activity has been associated with the presence of flavone glycosides, such as isovitexin-2-*O*-rhamnoside, kaempferol-3-*O*-rhamnoside, and quercetin-3-*O*-rhamnoside found in the ethyl acetate extract [102]. The flavonoid content is higher in *E. altissima* compared to *E. alata*. This has been evidenced when comparing the seeds of the two plants (both collected in Southern Tunisia). The former contained significantly more flavonoids but also more polyphenols and more condensed tannins than the latter species. As a result, the antioxidant potential of an *E. altissima* seed extract was found to be markedly higher than that of an *E. alata* seed extract. The predominant bioactive natural products were gallic acid, quercetin, epicatechin, naringin, and the atypical flavone cirsiol (3',4',5-trihydroxy-6,7-dimethoxyflavone) [31] (► **Fig. 4a**). Cirsiol is an interesting compound regulator of mitophagy in cancer cells [103], apparently acting as an inhibitor of tyrosine kinase TYK2 ($K_D = 0.8 \mu\text{M}$) in cancer cells and tumors [104]. Its anticancer effects have been well evidenced using different cell lines and tumor models in recent years [105, 106]. It is also a potent antioxidant molecule capable of binding to the enzyme F_1F_0 -ATP synthase [107] and a compound that can mitigate amyloid- β ($A\beta$) aggregation, therefore being of potential interest to treat neurodegenerative disorders [108]. This compound is probably a major contributor to the bioactivities of *E. altissima*.

The plant contains many other compounds, including alkaloids, tannins, saponins, and cardiac glycosides, identified after extraction with various organic solvents, notably with the plant leaves extracted with ethanol [109]. Phenols, sterols, saponins, tannins, terpenoids, flavonoids, and alkaloids have also been identified in an *E. altissima* stem methanolic extract, and this extract was found to affect male mice reproductive functions [110]. The same methanolic extract was found to exhibit a dose-dependent (500–3000 mg/kg) central nervous system depression and a mild antipsychotic activity without anxiolytic-like effects in mice [111]. It is interesting to note that the fresh stems of this species contain



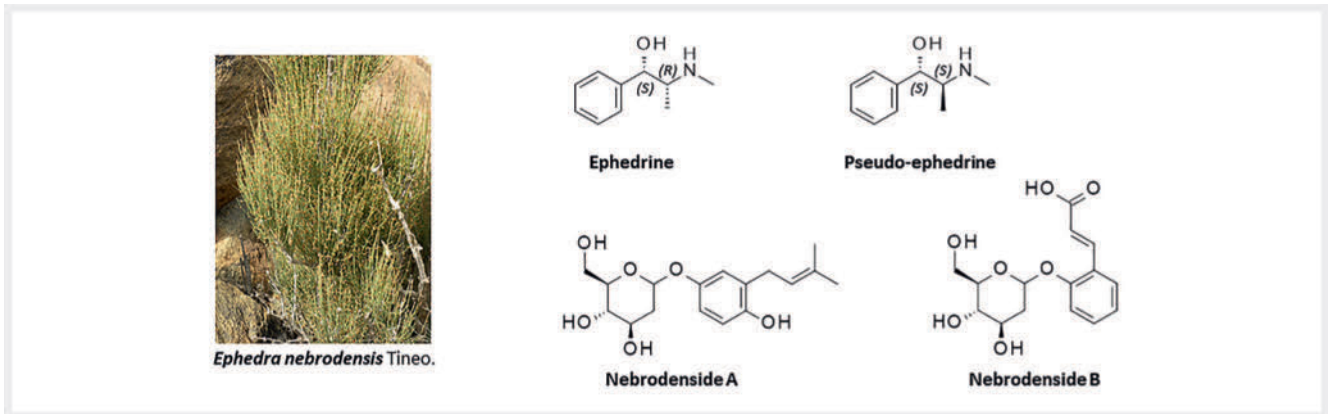
► **Fig. 4** *E. altissima* with the extraction process used to extract various natural products from the seeds, including the flavonoid cirsiol or the glutamate uptake inhibitor L-CCG III (*cis*- α -(carboxycyclopropyl) glycine) from the fresh stems of the plant (photo of the plant from <https://www.teline.fr>; photo credit: Jean-Claude Thiaudière).

neither ephedrine nor pseudoephedrine, but they contain substantial amounts of the two *cis*-diastereoisomers of the L-glutamate analogue (2*S*,3*S*,4*R*)-2-carboxycyclopropyl-glycine (L-CCGIII) and (2*S*,3*R*,4*S*)-2-(carboxycyclopropyl) glycine (L-CCGIV) (► **Fig. 4b**). These two rare 2-(carboxycyclopropyl)-glycine (CCG) derivatives (which constitute about 1% of the stem dry weight in the plant) alter neurotransmission. They selectively activate subgroups of glutamate receptors depending on stereochemistry. In mammalian neurons, L-CCGIII potentiates responsiveness to L-glutamate and L-CCGIV activates the *N*-methyl D-aspartate (NMDA) subtype of the L-glutamate receptor [112]. These compounds provided the foundation for the design of novel modulators of NMDA receptors [113].

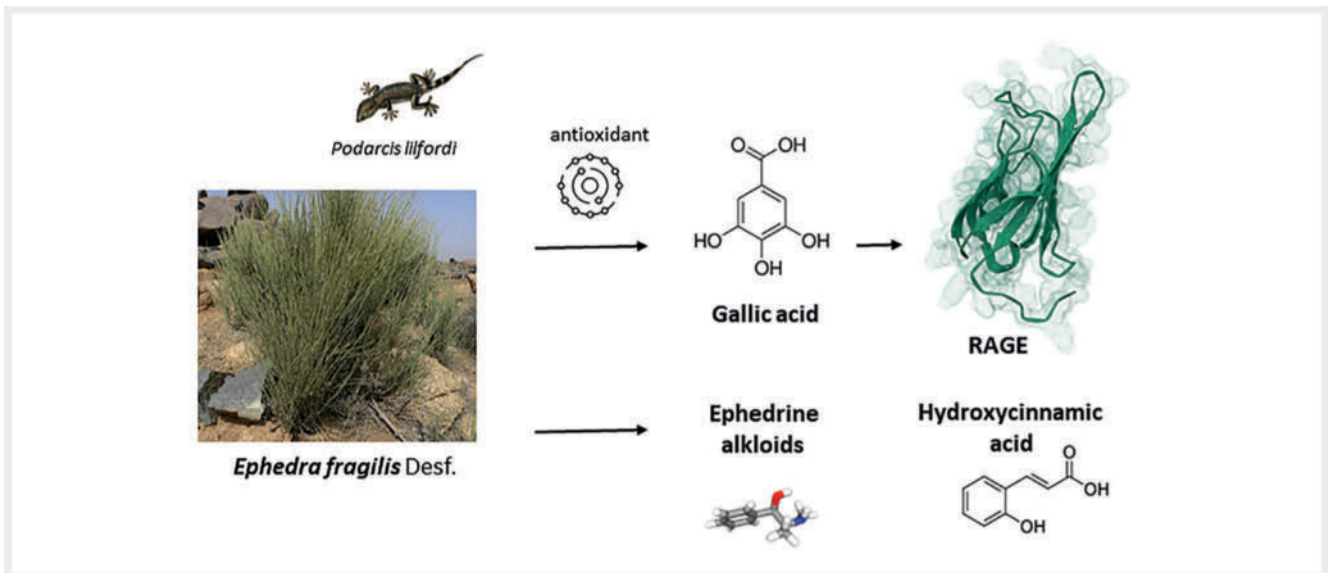
Ephedra nebrodensis Tineo (ex Guss.).

This *Ephedra* species is a Mediterranean medicinal plant well distributed in Morocco and Algeria and is also found in Italy. It is a Macaronesian-Mediterranean nanophanerophyte growing in dry and rocky places [114]. A 1:1 ethanolic:acetone crude extract prepared from the aerial parts of a plant sample collected in Urzulei (Sardinia, Italy) has shown antioxidant and hypotensive effects, as well as antinociceptive and anti-inflammatory activities. The presence of ephedrine-type alkaloids was suspected [59]. The presence of ephedrine and pseudoephedrine (► **Fig. 5**) was evidenced later when Hamoudi and coworkers performed a phytochemical screening of the same plant (aerial parts) collected in Algeria. They identified the alkaloids together with phenolic compounds and a large fraction of flavonoids with antioxidant properties [29,61]. They further characterized the antioxidant, anti-inflammatory, and analgesic effects of a hydroalcoholic extract of

E. nebrodensis, notably a marked dose-dependent capacity to reduce croton oil-induced ear edema in mice. The antioxidant effect has been correlated to the high content of polyphenolics, flavonoids, and tannins [30,61]. Cell protective effects were also observed. A 1:1 ethanolic:acetone extract from the aerial parts of the plant (collected from Arzana Province, Sardinia, Italy) has shown a protective effect against cardiovascular damages induced by the anticancer drug doxorubicin in rats. The level of the antioxidant defense enzymes (GSH and SOD) was increased and lipid peroxidation was reduced [115]. A phytochemical analysis performed using an essential oil from the related species *E. nebrodensis* Tineo ex Guss. subsp. *nebrodensis* (from Italy) has shown the presence of numerous volatile sesquiterpene hydrocarbons (citronellol, β -patchoulene, etc.) [116, 117]. Much the same type of terpenes have been found in other *Ephedra*-based volatile oils, such as (E)-phytol (10.1% in the oil of *E. fragilis*), and benzaldehyde and *cis*-calamenene (8.0 and 3.6%, respectively, in the oil of *E. distachya*) [118]. Two phenolic glycosides designated nebrodensides A and B (► **Fig. 5**) have been isolated from the aerial parts of this plant, together with (–)-epicatechin and (–)-ephedrine. The two compounds were found inactive against proliferation of Madin-Darby canine kidney (MDCK) cells and the influenza A virus [58]. Nebrodenside A has been found in *Dodonaea viscosa* (L.) (Spindacea) and shown to exert anti-inflammatory and analgesic properties [119]. The compound has been isolated from the herb *Leontopodium leontopodioides* (Willd.) Beauv. (Asteraceae) and characterized as a modest inhibitor of lipase and α -glucosidase enzymes (IC_{50} = 12.3 and 6.1 μ M, respectively) [120]. The same product was isolated from the aerial parts of *Phagnalons ordidum* L. (also Asteraceae) and shown to exert antioxidant activity [121]. Re-



► **Fig. 5** *E. nebrodensis* and the chemical structures of alkaloids ephedrine and pseudoephedrine and the two phenolic glycosides nebrodensides A–B (photo of the plant from <https://www.teline.fr>; photo credit: Jean-Paul Peltier).



► **Fig. 6** *E. fragilis* (stems) with a representation of the frugivorous lizard *Podarcis lilfordi*, which consumes the plant seeds and importantly contributes to their dispersion. The phenolic compound gallic acid (isolated from the stems) contributes to the antioxidant properties of the extract through interaction with the receptor for advanced glycation end products (RAGE; molecular structure from PDB: 2MOV) (photo of the plant from <https://www.teline.fr>; photo credit: Jean-Paul Peltier).

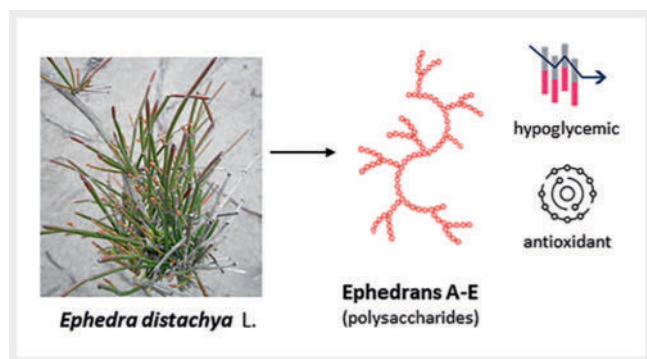
cently, a computational study has suggested that this compound could be used as an inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for COVID-19, owing to its capacity to bind to the receptor-binding domain of the virus Spike glycoprotein [122].

Ephedra fragilis Desf.

The evergreen species *E. fragilis* (vernacular name: joint pine) is a fleshy-fruited tall scrambling shrub (up to 1.8 m) growing essentially on rocky hills and stone walls. It is native to the eastern Mediterranean region of southern Europe and Northern Africa, and from Madeira and the Canary Islands (Spain). It grows primarily in the subtropical biome. Small animals are important contribu-

tors to the dispersion of the plant seeds, such as the frugivorous Balearic lizard *Podarcis lilfordi* Günther (Lacertidae) [123,124]. Through its intense frugivorous activity, this lizard plays a more important role than insects in pollination and seed dispersal [125] (► **Fig. 6**).

In Morocco, the plant can be found in the Souss-Massa region (Taroudant Province). An authenticated sample collected in the city of Oulad Teima, near Taroudant, has led to the preparation of an ethanolic extract further fractionated using ethyl acetate (EA). This EA fraction has revealed a high content of phenolic and flavonoid compounds and strong antioxidant activity. The fraction protected cultured cells (from *Tetrahymena pyriformis*) against oxidative stress injury induced by hydrogen peroxide, protecting



► **Fig. 7** *E. distachya* (stems) from which the polysaccharides ephedrans A–E can be isolated. These water-soluble polymers exhibit antioxidant and hypoglycemic properties [35] (photo of the plant from <https://inpn.mnhn.fr>; photo credit: P. Rouveyrol).

these cells from DNA damage and metabolic oxidation. The extract showed potent antioxidant activities [55]. The extraction process has been optimized and several bioactive compounds were isolated from the modified EA fraction, notably four phenolic compounds (caffeic acid, ferulic acid, gallic acid, and vanillic acid) and two conventional flavonoids (rutin and quercetin). The phenolic derivatives were characterized as the main components responsible for both antioxidant and antiglycation activities of the extract [83]. A complementary molecular modeling analysis (*in silico*) suggested that gallic acid can form stable complexes with the receptor for advanced glycation end product (RAGE) [83] (► **Fig. 6**). This is not surprising because these phenolic derivatives present high affinities for the different proteins of the HMGB1/RAGE/NF- κ B signaling pathway and gallic acid is known to reduce the risk of AGE-mediated cellular complications, preventing fibrosis induced by advanced glycation end products [126–128].

Total organic carbon (TOC) is particularly high in *E. fragilis* compared to other plants growing on semiarid Mediterranean soils [129]. Nevertheless, this species contains many less phenolic compounds than the other studied *Ephedra* species (notably 8-fold less phenols than *E. alata*) and less flavonoids as well, but a high content in ephedrine alkaloids [43]. The main characteristic of *E. fragilis* is the presence of the two alkaloids, pseudoephedrine and ephedrine, in the different parts of the plants. Pseudoephedrine is a stereoisomer of ephedrine (► **Fig. 5**) that is commonly used as a nasal decongestant in combination with other anti-inflammatory drugs for the symptomatic treatment of some common pathologies such as the common cold. The alkaloid content is very high in *E. fragilis* flowers, which contain both alkaloids (1.86%) whereas the seeds essentially contain pseudoephedrine (0.62%) and the branches a little quantity of ephedrine (0.054%), as determined with a specimen of *E. fragilis* from Malta [130]. Ephedrine and pseudoephedrine can exert immunomodulatory activities. Notably, pseudoephedrine has been shown to modulate T cell activation, via the inhibition of interleukin-2 (IL-2) and TNF- α gene transcription in stimulated Jurkat T cells, thereby inhibiting the transcriptional activity of proteins JNK and AP-1 (activator protein-1) [131]. Similar T cell deactivation effects have been re-

ported with caffeic acid [132]. It is therefore not surprising to observe that a plant extract containing the same type of phenolic compounds and alkaloids (with α -adrenoceptor activity) can also affect lymphocyte activities. Ephedrine has been shown to attenuate oxidative damages in epithelial cells, through regulation of endoplasmic reticulum (ER) stress [133].

Several studies have underlined the anti-inflammatory action of ephedrine and ephedrine-containing extracts from various *Ephedra* species [16, 134–136]. An extract of *E. fragilis* made from a Tunisian specimen revealed dose-dependent anti-inflammatory effects, with inhibition of the production of nitric oxide (NO) in lipopolysaccharide-stimulated RAW 264.7 macrophages. The ethanolic extract contained high levels of both caffeic acid and hydroxycinnamic acid [137]. This latter compound notoriously exerts antioxidant activity and modulates proinflammatory cytokines [138].

Ephedra distachya L.

This shrub species (also known as *Ephedra vulgaris* Rich. or sea grape) is a major component of desert vegetation. It can be found in North Africa (Morocco, Algeria) but also in sand dunes of temperate deserts, such as the Gurbantüggüt desert in the Junggar Basin (northwestern China), and in Central Asia, for example [139, 140]. It can be found as well in clay steppes of the Ulyanovsk region in Russia [141], the Balkan Peninsula in Serbia [142], and the dunes of Letea in Romania [143, 144].

From a phytochemical viewpoint, this species has been less investigated than the other aforementioned species. This herb is rich in catechins, which possess antioxidant activities [145], and also contains large amounts of pseudoephedrine (1.25–1.59% of dry weight), a sympathomimetic used to treat symptoms of the common cold and flu, sinusitis, asthma, and bronchitis [74]. The subspecies *E. distachya* subsp. *helvetica* (from Vienna, Austria) was shown to contain 20.8 mg of (pseudo)ephedrine per gram of dry weight, which is less than the content in *E. fragilis* (27.1 mg/g) [43]. However, the ephedrine content may vary substantially from one plant to another because another study indicated that ephedrine was not detected in the species *E. distachya* subsp. *helvetica* [146]. Its content in phenolic and flavonoid compounds is not particularly high (largely inferior to that found in *E. alata*, for example), but this species does present a high content of total alkaloids (15.8 mg/g compared to 0.2 mg/g in *E. fragilis*) [43]. These alkaloids have not been characterized formally but the phylogenetic similarities between *E. distachya* and the well-studied analogous species *Ephedra sinica* [147] suggest that it may contain similar alkaloids such as the ephedrannins largely present in *E. sinica* [148]. Cell suspension cultures (callus) of *E. distachya* have been developed and used to elicit the production of phytoalexin *p*-coumaroylamino acids by the addition of a yeast extract to the culture [149–151].

A characteristic of *E. distachya* is the content in glycans called ephedrans A, B, C, D, and E, with hypoglycemic and antioxidant activities [48] (► **Fig. 7**). They have a different molecular mass (from 6.6×10^3 to 1.5×10^6 Da) and varied monosaccharide compositions, with the presence of trehalose and xylose in ephedrans A and B, and various proportion of rhamnose and arabinose [148]. These polysaccharides also display anti-inflammatory activity

[152]. Similar polysaccharides with antihypertensive and antioxidant activities have been characterized in other species, such as *E. alata* [153].

Clinical trials with *Ephedra*-based products

Medicinal products containing *Ephedra* extracts or ephedrine are not frequently used nowadays due to the adverse effects reported with *Ephedra* preparations in the past (see Discussion below). However, there are rare clinical trials that concern *Ephedra*, notably with Chinese medicines containing Mahuang (*Ephedrae herba*). For example, trial NCT03733873 has evaluated the *Ephedra*-containing Chinese medicine Suoquan for the treatment of nocturnal enuresis [154]. Trial NCT00432991 evaluated the effect of intramuscular ephedrine on the incidence of nausea and vomiting in women during and after a Cesarean section. The objective was to reduce or prevent hypotension [155]. Ephedrine and phenylephrine can be safely used to counteract hypotension after spinal anesthesia in obstetric patients, but the safety of the product administration requires careful monitoring [156, 157]. We will not discuss further ephedrine-based trials so as to maintain a focus on *Ephedra* plants and extracts.

Discussion

Plants of the *Ephedraceae* family and *Ephedra* species in particular are used in many countries all over the world to treat human diseases. One of the most popular *Ephedra*-based medicinal herbs is the one called Mahuang in Chinese, which corresponds to the herbaceous stem of *E. sinica* Stapf, *Ephedra intermedia* Schrenk et C. A. Mey., and *Ephedra equisetina* Bge. [158]. Mahuang decoctions (*Ephedrae herba*) are largely used in China to treat asthma, liver disease, skin disease, and other diseases [4, 5]. *Ephedrae herba* (Maoto) is also used in traditional Japanese medicine (Kampo) [159, 160], based notably on the cultivation of *E. sinica* [161]. The same species is also used in the Republic of Korea, notably to combat obesity [162, 163]. *Ephedra* species can be found on all continents and many of them are associated with traditional medicinal usage. The bracts of *Ephedra* cones have played a crucial role in long-distance seed dispersal that is responsible for a wide distribution of the genus in semiarid and arid areas of Eurasia, North Africa, North America, and South America [164]. *Ephedra* species are commonly exploited for their anti-inflammatory, anticancer, antibacterial, antioxidant, hepatoprotective, anti-obesity, antiviral, and diuretic activities [11, 148]. To our knowledge, seven *Ephedra* species are present in Morocco, including five used traditionally to treat diverse symptoms and/or pathologies (Fig. ► 1). Four species are clearly listed as being used to treat inflammatory diseases (such as rheumatism) or other pathologies: *E. alata* (the most frequently used species), *E. altissima*, *E. fragilis*, and *E. nebrodensis*. The ethnobotanical use of *E. distachya* in Morocco is very likely, but firm evidence is lacking. Nevertheless, this species is with no doubt a medicinal plant used in the surrounding Mediterranean area.

The medicinal activities of Moroccan *Ephedra* extracts can be linked to the presence of diverse bioactive products, in particular ephedrine-type alkaloids and glycosylated flavonoids. Among the many beneficial flavonoids, one can underline the anti-inflamma-

tory action of isoschaftoside found in *E. alata*, for example [95]. This compound is a potent antioxidant and an anti-inflammatory agent with an anti-steatosis activity useful to combat metabolic liver disease [165, 166]. Other flavonol glycosides, such as isorhamnetin-3-*O*-rutinoside, contribute similarly to the antioxidant and anti-inflammatory effects [16]. This compound is also a pro-apoptotic agent, useful to limit the growth of cancer cells [167]. It would be interesting to apply network pharmacology approaches to determine how these different metabolites participate and cooperate to promote the activity of the plant extract. This type of approach has proved useful to predict the combinatorial effects of *Ephedrae herba* components [162, 168–170].

Evidently, alkaloids are essential components of the extracts, most of them containing either ephedrine and/or pseudoephedrine. Their content varies from one *Ephedra* species to another, depending on diverse plant growth parameters, such as altitude. It has been observed recently with another species (*Ephedra saxatilis*) that the ephedrine content increased as the altitude gradient increased, and pseudoephedrine decreased as the altitude gradient decreased [171]. There is also a seasonal variation of the alkaloid content [161]. Their concentrations vary greatly according to plant species, the collection location, and cultivation conditions [172, 173]. Both ephedrine and pseudoephedrine are key medicinal components of almost all *Ephedra*, and their contents in *Ephedra* formulations can be precisely estimated from the compounding amount of the starting *Ephedra* plant [160]. They are useful medications to prevent or treat hypotension, for example, owing to their indirect sympathomimetic pharmacodynamic properties [174] but their use remains controversial, because they can also induce cardiovascular side effects, including stroke and heart attack [175, 176]. Pseudoephedrine was considered potentially more useful than ephedrine due to its anorexigenic effect and its capacity to influence lipolysis and thermogenesis. But the use of this product is also associated with effects on the cardiovascular and central nervous systems. Its prescription to obese patients is not at all recommended [177]. These considerations have prompted the development of ephedrine alkaloid-free *Ephedra* herb extracts [21, 24, 178]. Beyond flavonoids and alkaloids, *Ephedra* extracts also contain useful terpenoids, carboxylic acids, tannins, and other types of constituents such as unsaturated fatty acids [55, 97, 179, 180]. The polysaccharides found in the stems of *E. alata* are particularly interesting products due to their contribution to the antihypertensive and antioxidant activities of the extracts [153]. *Ephedra* polysaccharides warrant further consideration to improve their identification and contribution to extract activities [181, 182].

Ephedrine was well recognized as a dependable asthma treatment in the Western world by the mid-1930 s. Primitive inhalers were created to provide ephedrine alkaloids, and they become the main oral asthma medications in the 1940 s and 1950 s [3]. Ephedrine was widely used and readily available, but over time, it was realized that the alkaloid was more toxic than initially thought.

Ephedra was appointed as a weight-loss and energy-enhancement supplement in the US in the 1990 s and early 2000 s. It was categorized as an herbal supplement under the Dietary Supplement Health and Education 1994 [183, 184]. No evidence

proved *Ephedra*'s effectiveness other than short-term weight loss. However, the number of reported adverse events increased [185]. In 2004, the Food and Drug Administration (FDA) in the United States received over 18 000 reports of harmful events associated with *Ephedra*, and banned dietary supplements with ephedrine alkaloids [4, 185]. The same ban of *Ephedra* was imposed in the European Union by the European Commission in 2015. Among the toxic responses to *Ephedra* use are increased blood pressure, excitement, sweating, and dysuria, in addition to more serious events like arrhythmia, nephritis, gallstones, and possibly death due to myocardial infarction and stroke or respiratory failure [4, 183, 184].

Altogether, our analysis identified the *Ephedra* species used traditionally in Morocco and provided useful information to establish links between the pharmacological effects observed with the plant extracts and the nature of bioactive natural products identified in those preparations. Moroccan *Ephedra* plants, notably the two most frequently used regional species *E. alata* and *E. altissima*, represent key medicinal plants for the country. Their traditional use can be encouraged, but always with caution due the presence of potentially harmful ephedrine-type alkaloids [18, 183, 185]. Their use should be accompanied with health information whenever possible. In this respect, the danger of using Arabic YouTube videos regarding herbal cancer treatment has been pointed out recently [186]. There is no reason to ban the traditional use of Moroccan *Ephedra* extracts to treat some human infections, notably inflammatory symptoms, making profit of the abundance, relative safety, and beneficial functional attributes of the products. But it would be useful to assess the toxicological profile of such extracts in parallel, so as to better understand the efficacy, safety, and quality of the available products.

Finally, beyond the health benefits, it is interesting to note that the same type of Moroccan *Ephedra* extracts can be used in the field of green chemistry. An aqueous plant extract of *E. alata* has proved efficient when used as a reducing and capping agent for the synthesis of copper oxide nanoparticles [187]. Similarly, other *Ephedra* extracts have been used to prepare various types of composite nanoparticles [187–190]. A bright future may be anticipated in front of *Ephedra* plant extracts in medicine, green chemistry, and the food industry.

Materials and Methods

The scientific literature pertaining to *Ephedra* species found in Morocco was searched through the databases of PubMed Central, Web of Science, and Google Scholar. The article search was performed essentially from January to September 2023, using individual key words (*Ephedra*, *Ephedrae herba*, ephedrine, *Ephedra* alkaloids) and combinations to cover all scientific data reported thus far on the plant family. Databases from various publishers, such as ScienceDirect, Springer, Wiley, and others were also consulted. About 250 publications were reviewed and priority was given to the most recent studies. Publications (mostly in the English language) and written information (including those in Arabic language) providing a precise location of the plant were taken into consideration. Other studies not specifying the geographical origin of the plant were only considered for analysis of the phyto-

constituents and their mechanism of action. The validated names of the different *Ephedra* species have been checked (<http://www.worldfloraonline.org>, accessed on September 10, 2023).

Conclusion and Outlook

Five medicinal *Ephedra* species present in Morocco were identified, namely, *E. alata*, *E. altissima*, *E. distachya*, *E. fragilis*, and *E. nebrodensis*. They are used locally in the Moroccan traditional pharmacopeia to treat a variety of human diseases, such as asthma, rheumatism, hypertension, diabetes, cancer, and other pathologies. The pharmacological evidence necessary to support their clinical use remains somewhat insufficient at present for these Moroccan species. Further studies are encouraged to better support the medicinal use of these plants.

Contributors' Statement

Data collection: M. Chroho; Design of the study: C. Bailly, L. Bouissane; Drafting the manuscript: M. Chroho, C. Bailly, L. Bouissane; Investigation: C. Bailly, L. Bouissane; Visualization: C. Bailly, L. Bouissane; Revision and editing of the manuscript: L. Bouissane; Supervision of the final version of the manuscript: C. Bailly, L. Bouissane.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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