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A comprehensive review on ethnobotanical, phytochemical and pharmacological aspects of the genus *Dorema*

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Abstract The genus *Dorema* (Apiaceae) comprises 12 accepted species, mainly growing in Asia and, particularly, in Iran, where *D. ammoniacum* and *D. aucheri* are the most used species in cuisine and folk medicine. The *Dorema* species are traditionally applied in the treatment of catarrh, asthma, chronic bronchitis, as carminative, mild diuretic and anthelmintic agents. In general, 42 non-volatile secondary metabolites were isolated from the 6 studied species, namely *D. aitchisonii, D. ammoniacum*, *D. aucheri*, *D. glabrum*, *D. hyrcanum*, and *D. kopetdaghense*. Among them, phenolic acid, flavonoid, acetophenone, coumarin, and sesquiterpene derivatives were identified as the predominant phytoconstituents. The leaves are characterized by the highest volatile content, and the sesquiterpenes in both hydrocarbon and oxygenated forms were reported as the most abundant compounds. Most of the studied pharmacological activities were assessed in vivo. Nevertheless, in vitro antiradical and antimicrobial potentials were the main investigated activities. Overall, the evaluation of bioactivities confirmed the ethnopharmacological use of the *Dorema* species, particularly their anti-inflammatory, antibacterial, and hypolipidemic properties. This study comprehensively overviewed, for the first time, the literature relating to the folk medicinal use and to the available phytochemical and pharmacological data. Considering the genus application and the rare clinical trials, the study of the efficacy and safety of the uninvestigated *Dorema* species might be an interesting and promising approach for further researches.

Keywords *Dorema* · Apiaceae · Endemic Iranian plants · Folk medicinal use · Pharmacology · Phytochemistry

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Introduction

The family Apiaceae is considered one of the largest families in the plant kingdom, usually known as parsley, carrot or celery family, comprising 418 genera and 3257 species (http://www.theplantlist.org), predominantly aromatic plants with hollow

stems. Several species are consumed as vegetables or condiments and some of them possessing medicinal properties (Tamokou et al. 2017).

Although some studies suggested that *Dorema* spp. should be taxonomically subsumed within genus *Ferula* (Shneyer et al. 1995; Panahi et al. 2015, 2018), other ones considered *Dorema* as a distinct genus. Anyway, the plants possess thickened storage roots and large simple umbels with male flowers on the lower branches and hermaphrodite flowers on the upper branches. They are monocarpic and can reach 3 m in height with stem diameter of 10 cm or more (Schischkin et al. 1951; Pimenov and Leonov 1993).

The genus *Dorema* includes 12 accepted species mostly distributed in the southern regions of central western Asia such as Caucasus, Iran, Afghanistan, and Pakistan (http://www.theplantlist.org) (Schischkin et al. 1951; Pimenov and Leonov 1993). Among them, 7 species, namely *D. aitchisonii* Korovin ex Pimenov, *D. ammoniacum* D. Don, *D. aucheri* Boiss., *D. aureum* Stocks, *D. glabrum* Fisch. & C.A. Mey., *D. kopetdaghense* Pimenov and *D. hyrcanum* Koso-Pol., belong to Iranian flora (Rechinger and Hedge 1987; Mozaffarian 2003, 2007). In particular, *D. ammoniacum* and *D. kopetdaghense* are endemic to Iran and their oleo gum resin is used for 4000 years (Hooper 1937; Duthie 1956; Jafari et al. 2004). *D. ammoniacum* (local names: *Ushaq*, *Oshagh*, *Vasha*, and *Kandal*) and *D. aucheri* (local name: *Bilhar*) are widely consumed in cuisine as food and additive. In folk medicine, the *D. ammoniacum* resin, commonly known as "ammoniacum" or "gum ammoniac", is traditionally collected for several purposes including the treatment of the respiratory, digestive and urinary systems. It is also mentioned in Unani Medicine or Greco-Arab Medicine, one of the oldest traditional medicines, as a potent drug useful for various ailment and diseases (Mobeen et al. 2018) as reported by Avicenna (1930) and Al-Razi in their treatises (Razi and Kitab 1991; Baitar 1999).

Coumarin, sesquiterpene and flavonoid derivatives were identified as the major phytochemicals of the genus *Dorema*. Sesquiterpenes in both hydrocarbon and oxygenated forms were described as the predominant volatile oil compounds characterizing various plant parts.

In recent years, the number of papers reporting experimental data on the biological effects of *Dorema* species has increased. However, there is no available systematic review that summarizes current knowledge. Due to widespread traditional use of these plant species, the present work aimed to comprehensively collect the published studies on their ethnobotanical use, phytochemical and pharmacological features, for the first time. A literature search was carried out (last search: 01.03.2020) using the PubMed and Web of Science databases with "*Dorema*" as keyword.

Traditional uses of *Dorema* species

Table 1 lists the ethnomedicinal uses of the *Dorema* species. The most used part is the oleo gum resin which is mainly obtained from stem, root and petiole parts. In Iran, the resin from *D. ammoniacum* is used for its expectorant, anticonvulsant, anthelmintic, antimicrobial, anti-inflammatory, analgesic, vasodilator, carminative, mild diuretic, antispasmodic and diaphoretic properties, as well as for the treatment of chronic bronchitis, persistent coughs, respiratory and gastrointestinal disorders (Rajani et al. 2002; Mood 2008; Irvani et al. 2010; Nabavi et al. 2012; Adhami et al. 2013; Hosseini et al. 2014; Ajani et al. 2018; Ghasemi et al. 2018). According to the British Herbal Pharmacopoeia (1983, 1993), the same resin is also useful as a hepatoprotective, sudorific, sedative and sexual stimulant agent, to regulate the menstrual cycle, reduce blood fats and prevent diabetes. Otherwise, the *D. ammoniacum* young leaves and branches are harvested to cure digestive disorders, as well as to be preserved pickled for eating (Ajani and Bockhoff 2018). The seeds are collected to treat respiratory disorders (Abedini et al. 2014).

The efficacy of *D. ammoniacum* in livestock was also reported. Both resin and roots are used to heal infected wounds and abscesses in sheep and goats (Amiri and Joharchi 2016).

D. aucheri is the second most used *Dorema* species in Iranian folk medicine. A fresh root-based paste is used locally as a remedy in the healing of burns, while the resin is administered orally against asthma, bronchitis, as an expectorant and for its antispasmodic properties. Resin roots are also applied to infected sheep wounds. On the other hand, the young aerial parts are used against disorders due to constipation and parasites in the digestive system. In cuisine, they are used in the preparation of typical soups or pickles (Amiri and Joharchi 2016; Akbarian et al. 2016; Ajani and Bockhoff 2018). For this species, the ability to

Table 1 Ethnobotanical uses of *Dorema* species

Dorema species	Ethnobotanical uses	Plant part	Plant preparation	Place/ Source	References
D. ammoniacum	Treatment of asthma, colics, cystitis, digestive disoders, furuncles, indolent tumours, anthelmintic, anticonvulsant, emmenagogue, expectorant, laxative (human); healing of infected wounds, against abscess in the sheep and goat (animal)	Resin, R	Infusion, poultice	Iran	Amiri and Joharchi (2016)
	Treatment of chronic bronchitis and persistent coughs, expectorant, mild diuretic, antispasmodic and stimulant, diaphoretic and emmenagogue	Resin	Poultice	Iran	Mood 2008 Hosseini et al. (2014)
	Carminative, diaphoretic, mild diuretic, expectorant, stimulant, antimicrobial, vasodilator	Resin	Nd	Iran	Irvani et al. (2010)
	Antispasmodic and expectorant Treatment of digestive disorders; food (pickles)	Resin, Young L, B	Nd	Iran	Ajani and Bockhoff (2018)
	Anti-inflammatory and analgesic effect	Resin	Nd	Iran	Bakhtiarian et al. (2017)
	Anticonvulsant	Resin of S and L	Nd	Iran	Motevalian et al. (2017)
	Treatment of dermatitis, inflammation, spasm, asthma and bronchitis, infectious diseases	Nd	Nd	Iran	Rabe et al. (2015)
	Treatment of respiratory disorders	Se	Nd	Iran	Abedini et al. (2014)
	Expectorant, stimulant, antispasmodic	Resin	Nd	Iran	Rajani et al. (2002) Nabavi et al. (2012) Adhami et al. (2013)
	Expectorant, stimulant, antispasmodic	Resin	Nd	India	Kumar et al. (2006)
	Treatment of asthma, catarrh, chronic bronchitis; against enlargement of liver and spleen	Resin of S and L	Nd	Iran	Rajani et al. (2002)
	Antimicrobial, anti-inflammatory, carminative, diaphoretic, mild diuretic, expectorant, stimulant, vasodilator agent, antispasmodic and expectorant, treatment of chronic bronchitis and persistent coughs; cosmetic, detergent and food	Resin of S, R, and P	Poultice	Iran	Yousefzadi et al. (2011) Zandpour et al. (2018) Mazaheritehrani et al. (2020) Pandpazir et al. (2018)
	Anthelmintic and for gastrointestinal disorders, anticonvulsant	Resin of S and R	Nd	Iran	Adhami et al. (2013) Ghasemi et al. (2018)
	Treatment of catarrh, asthma, enlargement of liver and spleen, gastric disorders, intestinal parasitic infections, skin inflammations, analgesic and laxative	Resin of S, R, and P	Nd	Iran	Mazaheritehrani et al. (2020)

Table 1 continued

Dorema species	Ethnobotanical uses	Plant part	Plant preparation	Place/Source	References
	Antibacterial, antifungal, carminative, stimulant; diaphoretic, diuretic, and anti-spasmodic activity; treatment of bronchitis and sever coughs	Nd	Nd	Iran	Tavakkoli et al. (2020)
	Treatment of dermatitis; anti-inflammatory and antispasmodic agent	Resin	Nd	Iran	Iranshahi et al. (2007)
	Treatment of spastic pains, gastric disorders, intestinal parasitic infections, skin inflammations, catarrh, asthma, chronic bronchitis and persistent cough; analgesic, stimulant, laxative, diaphoretic and emmenagogue	Resin	Nd	Iran	Masoudi and Kakavand (2017) Zandpour et al. (2016)
	Sputum containing horny sputum, cough irritant, sudorific, the regulation of menstrual, reducer of blood fats, prevention of diabetes, hepatoprotective mechanism, sexual stimulus and sedative	Resin of S	Nd	British Pharmacopeia	Zandpour et al. (2016)
D. aucheri	Food	Young AP	Boiled in soup or boiled and then fried	Iraq	Pieroni et al. 2017
	Treatment of asthma, expectorant, bronchitis, parasites of digestive system, constipation, burns; food (edible, use as vegetable, young stems are pickled) (human); treatment of infected wound healing and infection in sheep (animal)	Resin, young AP, R	Fresh paste	Iran	Abedini et al. 2014
	Antispasmodic and expectorant Treatment of digestive disorders; pickle	Resin, Young L, B	Nd	Iran	Ajani and Bockhoff (2018)
	To lower the blood pressure; food	Nd	Nd	Iran	Mianabadi et al. (2015)
	Treatment of microbial infections	R	Nd	Iran	Sepahi et al. (2015)
	Stimulant, nervonic, antispasmodic, bronchodilator, expectorant, kidney stone repellent, emmenagogue and analgesic for visceral pain; food	Nd	Nd	Iran	Khanahmadi et al. 2012
	To control diabetes mellitus, decrease the blood triglycerides and modulate pain	Nd	Nd	Iran	Mostafavi et al. (2013) Vani et al. (2019)
	Food, food additive Treatment of microbial infections To control diabetes and reduce pain	L R Nd	Nd	Iran	Akbarian et al. (2016)
D. glabrum	Diuretic and antidiarrheal, treatment of bronchitis and catarrh, anticancer; used as a green vegetable	Resin, L	Nd	Iran	Delnavazi et al. (2015a,b)

AP: aerial parts; B: branches; P: petiole; L: leaves; Nd: not determined; R: roots; S: stems; Se: seeds

reduce blood pressure and triglycerides, as well as to modulate pain, is also recorded (Mostafavi et al. 2013; Vani et al. 2019).

Diuretic and anti-diarrheal potential, along with treatment of bronchitis and catarrh, were described for *D. glabrum* leaves and resin (Delnavazi et al. 2015a,b).

Conversely, the use of *Dorema* species is rather limited in other Asian countries. In the Iraqi Hawraman area (Kurdistan), only the young aerial parts from *D. aucheri* (local name: *Bana*) are used as food (Pieroni et al. 2017), while in India, the resin is renowned for its expectorant, stimulant, and antispasmodic effects (Kumar et al. 2006).

Phytocostituents

Non-volatile components

In general, half of the accepted *Dorema* species (6 out of 12) were studied for their non-volatile composition. Totally, 10 phenolic acids (**31**–**40**), 7 flavonoids (**10**–**16**), 7 acetophenones (**17**–**23**), 6 coumarins (**4**–**9**), 7 sesquiterpenes (**24**–**30**), 3 chromandiones (**1**–**3**), and 2 phytosterols (**41**–**42**) were identified as the main secondary metabolites (Table 2).

Coumarin and acetophenone derivatives were isolated from 4 (*D. ammoniacum*, *D. glabrum*, *D. hyrcanum* and *D. kopetdaghense*) and 3 species (*D. aitchisonii*, *D. glabrum* and *D. hyrcanum*), respectively. Chromandione derivatives were identified only in the resin of *D. ammoniacum*. Most of the coumarins were found in the roots, gum-resin and aerial parts. The flavonoid presence was exclusively reported in the aerial parts, extracted both with chloroform ($CHCl_3$) and methanol (MeOH). Otherwise, acetophenones were only detected in the MeOH extract obtained from the roots, whereas the sesquiterpene derivatives were mostly isolated from their $CHCl_3$ extract. Moreover, all plant parts (whole aerial parts, flowers, leaves, roots and stems) were rich in phenolic acids. The chemical structures of the identified non-volatile secondary metabolites of the *Dorema* species are illustrated in Fig. 1a, b.

Prenylated chromandiones

A new prenylated chromandione (2′S,5′S)-2′-ethenyl-5′-(3-hy-droxy-6-methyl-4-oxohept-5-en-2-yl)-7-methoxy-2′-methyl-4H-spiro[chromene-3,1′-cyclopentane]-2,4-dione (**1**) and doremone A (**2**) were isolated from dichloromethane (DCM) extract of *D. ammoniacum* resin (Arnone et al. 1991; Adhami et al. 2013), while ammodoremin (**3**) was obtained from *n*-hexane extract. It is an epimeric mixture of prenylated chromandiones whose structures were established by spectral data and single-crystal X-ray analysis (Appendino et al. 1991). The compound (**1**) was identified as an analogue of (**2**).

Coumarins

The coumarin 6,7,8-trihydroxycoumarin (**4**) was finally isolated by chromatography on a RP-18 column from the MeOH extract of *D. glabrum* roots (Delnazavi et al. 2015). Ammoresinol (**5**) was identified as a simple coumarin derivative, with a significant yield from DCM (Adhami et al. 2013) and *n*-hexane (Appendino et al. 1991) extracts of *D. ammoniacum* resin. From the same *n*-hexane extract, 7-hydroxyferprenin (**6**) was also obtained (Appendino et al. 1991).

Three other coumarin analogues were identified in two *Dorema* species. 3-Dihydro-7 methoxy-2S*,3R*-dimethyl-2-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c] coumarin (**7**) was isolated from acetone fraction of *D. kopetdaghense* aerial parts (Iranshahi et al. 2007), as well as from *D. hyrcanum* MeOH extract (Naghibi et al. 2015). 2,3-Dihydro-7-methoxy-2S*,3R*-dimethyl-2-[4,8-dimethyl-3(E),7-nonadien-6-onyl]-furo[3,2-c] coumarin (**8**) and 2,3-dihydro-7-methoxy-2R*,3R*dimethyl-2-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c] coumarin (**9**) were isolated from $CHCl_3$ and MeOH extracts of *D. kopetdaghense* (Iranshahi et al. 2007) and *D. hyrcanum* (Naghibi et al. 2015) roots, respectively.

Flavonoids

The aerial parts of *D. glabrum* and *D. aucheri* were investigated and 7 flavonoid derivatives were identified. Three glycosylated flavonols including isorhamnetin-3-*O*-β-D-glucopyranoside (**10**), isoquercetin (**11**), and astragalin (**12**) were obtained from MeOH extract of *D. glabrum* (Delnavazi et al. 2015b). Four flavones, namely salvigenin (**13**), nepetin (**14**),

Table 2 Non-volatile phytoconstituents isolated from the *Dorema* genus

No.	Class/compound name	Plant species	Plant part	Plant extract	References
Chromanndiones					
1	(2′*S*,5′*S*)-2′-Ethenyl-5′-(3-hy-droxy-6-methyl-4-oxohept-5-en-2-yl)-7-methoxy-2′-methyl-4*H*-spiro[chromene-3,1′-cyclopentane]-2,4-dione	*D. ammoniacum*	GR	DCM	Adhami et al. (2013)
2	Doremone A	*D. ammoniacum*	GR	DCM	Adhami et al. (2013)
				Nd	Arnone et al. (1991)
3	Ammodoremin	*D. ammoniacum*	GR	*n*-Hexane	Appendino et al. (1991)
Coumarins					
4	6,7,8-Trihydroxycoumarin	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
5	Ammoresinol	*D. ammoniacum*	GR	DCM	Adhami et al. (2013)
				n-Hexane	Appendino et al. (1991)
6	7-Hydroxyferprenin	*D. ammoniacum*	GR	*n*-Hexane	Appendino et al. (1991)
7	2,3-Dihydro-7-methoxy-2S*,3R*-dimethyl-2-[4,8-dimethyl-3(*E*),7-nonadienyl]-furo[3,2-c] coumarin	*D. kopetdaghense*	AP	Acetone	Iranshahi et al. (2007)
		D. hyrcanum	R	MeOH	Naghibi et al. (2015)
8	2,3-Dihydro7-methoxy-2S*,3R*-dimethyl-2-[4,8-dimethyl-3(*E*),7-nonadien-6-onyl]-furo[3,2-c] coumarin	*D. kopetdaghense*	R	$CHCl_3$	Iranshahi et al. (2007)
9	2,3-Dihydro-7-methoxy-2R*,3R*dimethyl-2-[4,8-dimethyl-3(*E*),7-nonadienyl]-furo[3,2-c] coumarin	*D. hyrcanum*	R	MeOH	Naghibi et al. (2015)
Flavonoids					
10	Isorhamnetin-3-*O*-β-D-glucopyranoside	*D. glabrum*	AP	MeOH	Delnavazi et al. (2015b)
11	Quercetin-3-*O*-β-D-glucopyranoside (isoquercetin)	*D. glabrum*	AP	MeOH	Delnavazi et al. (2015b)
12	Kaempferol-3-*O*-β-D-glucopyranoside (astragalin)	*D. glabrum*	AP	MeOH	Delnavazi et al. (2015b)
13	Scutellarein 6,7,4′-trimethyl ether (salvigenin)	*D. aucheri*	AP	$CHCl_3$	Wollenweber et al. (1995)
14	6-Methoxyluteolin (nepetin)	*D. aucheri*	AP	$CHCl_3$	Wollenweber et al. (1995)
15	6-Hydroxyluteolin 6,7-dimethyl ether (cirsiliol)	*D. aucheri*	AP	$CHCl_3$	Wollenweber et al. (1995)
16	6-Hydroxyluteolin 6,7,4′-trimethyl ether (eupatorin)	*D. aucheri*	AP	$CHCl_3$	Wollenweber et al. (1995)
Acetophenones					
17	Azeroside A	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
18	Azeroside B	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
19	Echisoside	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
					Jafari et al. (2018)
20	Pleoside	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
					Jafari et al. (2018)
21	Hyrcanoside	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
22	4-Methoxy-6-hydroxyacetophenone-2-*O*-β-D-gentiobioside	*D. hyrcanum*	R	MeOH	Naghibi et al. (2015)
23	2,6-Dihydroxy-4-methoxyacetophenone-2-*O*-β-gentiobioside	*D. aitchisonii*	R	Alcoholic	Bukreeva and Pimenov 1991
Sesquiterpenes					
24	Kopetdaghin A	*D. kopetdaghense*	AP	Acetone	Iranshahi et al. (2007)
			R	$CHCl_3$	Iranshahi et al. (2007)
25	Kopetdaghin B	*D. kopetdaghense*	AP	Acetone	(Iranshahi et al. (2007)
			R	$CHCl_3$	Iranshahi et al. (2007)

Table 2 continued

No.	Class/compound name	Plant species	Plant part	Plant extract	References
26	Kopetdaghin C	*D. kopetdaghense*	AP	Acetone	Iranshahi et al. (2007)
			R	$CHCl_3$	Iranshahi et al. (2007)
27	Kopetdaghin D	*D. kopetdaghense*	R	$CHCl_3$	Iranshahi et al. (2007)
28	Kopetdaghin E	*D. kopetdaghense*	R	$CHCl_3$	Iranshahi et al. (2007)
29	Naghibione	*D. hyrcanum*	R	MeOH	Naghibi et al. (2015)
30	Dshamirone	*D. ammoniacum*	GR	DCM	Adhami et al. (2013)
Phenolic acids					
31	Gallic acid	*D. aucheri*	L, S, Fl	MeOH	Mianabadi et al. (2015)
32	*p*-Coumaric acid	*D. aucheri*	L, Fl	MeOH	Mianabadi et al. (2015)
33	Ferulic acid-4-*O*-β-D-glucopyranoside	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
34	7,8-Dihydroferulic acid-4-*O*-β-D-glucopyranoside	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
35	Chlorogenic acid	*D. glabrum*	AP	EtOAc	Delnavazi et al. (2015a)
			R	MeOH	Delnavazi et al. (2015a)
		D. aucheri	L, S, Fl	MeOH	Mianabadi et al. (2015)
36	Caffeic acid	*D. aucheri*	L, S, Fl	MeOH	Mianabadi et al. (2015)
37	4,5-Di-*O*-caffeoylquinic acid	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
					Jafari et al. (2018)
38	3,5-Di-*O*-caffeoylquinic acid	*D. glabrum*	AP	MeOH	Delnavazi et al. (2015b)
39	5-*O*-Caffeoylquinic acid	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
40	1,5-Di-*O*-caffeoylquinic acid (cynarine)	*D. glabrum*	R	MeOH	Delnavazi et al. (2015a)
					Jafari et al. (2018)
			AP	MeOH	Delnavazi et al. (2015b)
Phytosterols					
41	Sitosterol 3-*O*-glucoside (daucosterol)	*D. kopetdaghense*	AP	Acetone	Iranshahi et al. (2007)
		D. glabrum	AP	EtOAc	Delnavazi et al. (2015b)
42	Stigmasterol 3-*O*-glucoside	*D. kopetdaghense*	AP	Acetone	Iranshahi et al. (2007)

AP aerial parts, *$CHCl_3$* chloroform, *DCM* dichloromethane, *EtOAc* ethyl acetate, *Fl* flowers, *GR* gum-resin, *L* leaves, *MeOH* methanol, *R* roots, *S* stems, *Nd* not determined

cirsiliol (**15**) and eupatorine (**16**), were identified in $CHCl_3$ extract from *D. aucheri* (Wollenweber et al. 1995).

Acetophenones

Seven glycosylated acetophenone derivatives were isolated from *Dorema* species. All the compounds were purified from root MeOH extracts. Azerosides A (**17**) and B (**18**) were obtained from *D. glabrum* for the first time as natural products, along with echisoside (**19**), pleoside (**20**) and hyrcanoside (**21**) (Delnazavi et al., 2015a; Jafari et al. 2018). 4-Methoxy-6-hydroxyacetophenone-2-*O*-β-D-gentiobioside (**22**) and 2,6-dihydroxy-4-methoxyacetophenone-2-*O*-β-gentiobioside (**23**) were also isolated from alcoholic

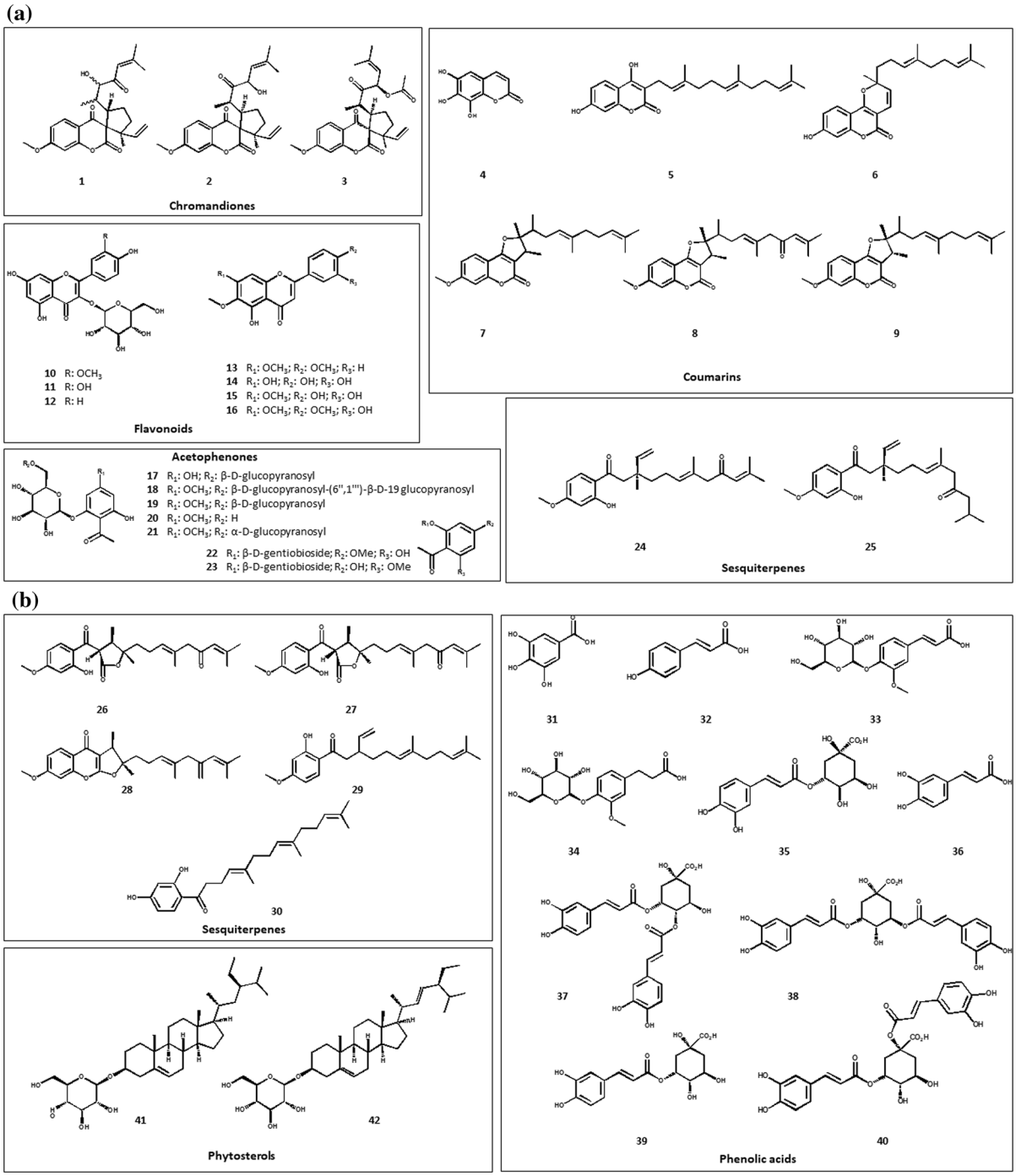

Fig. 1 **a**, **b** Chemical structures of the non-volatile phytochemicals isolated from *Dorema* species

extracts of *D. hyrcanum* (Naghibi et al. 2015) and *D. aitchisonii* (Bukreeva and Pimenov 1991), respectively.

Sesquiterpenes

Sesquiterpenes were identified as one of the predominant phytochemical classes in *Dorema* species. Three

new sesquiterpene derivatives namely kopetdaghin A (**24**), kopetdaghin B (**25**), and kopetdaghin C (**26**) were isolated both from aerial (acetone extract) and root ($CHCl_3$ extract) parts of *D. kopetdaghense* (Iranshahi et al. 2007). Furthermore, kopetdaghin D (**27**) and kopetdaghin E (**28**) were found in root $CHCl_3$ extract for the first time (Iranshahi et al. 2007). Naghibione (**29**) was also isolated in MeOH extract of *D. hyrcanum* root as a novel compound (Naghibi et al. 2015). Dshamirone (**30**) was isolated from the purified DCM extract of *D. ammoniacum* resin (Adhami et al. 2013).

Phenolic acids

Some phenolic acids were characterized starting from different parts of *D. aucheri* and *D. glabrum*. In the study of Mianabadi et al. (2015), HPLC fingerprinting analysis allowed to determine their presence in MeOH extracts obtained from *D. aucheri* stems, flowers and leaves, both from a qualitative and quantitative point of view. The stem extract was the richest sample in gallic acid (**31**) and chlorogenic acid (**35**). Otherwise, the highest contents of *p*-coumaric acid (**32**) and caffeic acid (**36**) were quantified in the flowers (Mianabadi et al. 2015). Chlorogenic acid (**35**) was furtherly isolated from ethyl acetate (EtOAc) (Delnavazi et al. 2015b) and MeOH (Jafari et al. 2018) extracts of *D. glabrum* aerial parts and roots, respectively. The MeOH extract of *D. glabrum* roots was previously studied leading to the isolation of acid-4-*O*-β-D-glucopyranoside (**33**) and 7,8-dihydroferulic acid-4-*O*-β-D-glucopyranoside (**34**) (Delnavazi et al. 2015a). Four caffeoylquinic acid derivatives were detected in *D. glabrum* MeOH extracts. They are 4,5-di-*O*-caffeoylquinic acid (**37**) and 5-*O*-caffeoylquinic acid (**39**) from the roots (Delnavazi et al. 2015a; Jafari et al. 2018), 3,5-di-*O*-caffeoylquinic acid (**38**) from the aerial parts (Delnavazi et al. 2015b) and 1,5-di-*O*-caffeoylquinic acid (**40**) both from roots and aerial parts (Delnavazi et al. 2015a,b; Jafari et al. 2018).

Phytosterols

By using various chromatography methods, sitosterol 3-*O*-glucoside (daucosterol) (**40**) from acetone and EtOAc extracts of *D. kopetdaghense* (Iranshahi et al. 2007) and *D. glabrum* (Delnavazi et al. 2015b) aerial parts, in addition to stigmasterol 3-*O*-glucoside (**41**) from acetone extract of *D. kopetdaghense*, were isolated as the only phytosterols identified in the *Dorema* genus.

Volatile components

Different plant parts (whole aerial parts, fruits, leaves, roots, stems and seeds) of the three most common *Dorema* species—*D. ammoniacum*, *D. aucheri* and *D. glabrum*—were analyzed for their essential oil content (EO) (Table 3).

Overall, all the studies were carried out on Iranian populations and the greatest EO content was found in the leaves. In particular, the highest and lowest yields were observed for EO of *D. ammoniacum* leaves (0.7%) (Yousefzadi et al. 2009, 2011; Masoudi and Kakavand 2017). Hydrocarbon and oxygenated sesquiterpenes were characterized as the major volatile oil compounds. β-Caryophyllene (3.54–3.54%), caryophyllene oxide (6.3−32.45%), (E)-β-ocimene (18.1−30.94%), and α-eudesmol (31.2%) were the most significant components (Yousefzadi et al. 2009, 2011; Akbarian et al. 2016; Zandpour et al. 2016; Masoudi and Kakavand 2017).

Figure 2 depicted the chemical structures of the main EO compounds in the *Dorema* species.

Pharmacological activities

Bioactivities of extracts, isolated secondary metabolites, oleo gum resin and essential oils of *Dorema* species were assessed by several research groups (Table 4). So far, six species were subjected to different in vitro and in vivo experiments. Two species—*D. ammoniacum* and *D. aucheri*—were extensively investigated, specifically their free radical scavenging and antimicrobial activities, probably due to the plant material availability and the wide applications in traditional medicine and cuisine.

In vivo studies on analgesic (*D. ammoniacum*), anticonvulsant (*D. ammoniacum*), antidiabetic (*D. ammoniacum*, *D. aucheri*), anti-inflammatory (*D. ammoniacum*), anti-plasmodial (*D. hyrcanum*), antiproliferative and cytotoxic (*D. aucheri*), antithyroid (*D. aucheri*), hepatotoxic (*D. aucheri*), hypolipidemic (*D. aucheri*), neuroprotective (*D. ammoniacum*), and vascular toxic (*D. ammoniacum*) effects were carried out. Furthermore, antiradical (*D. ammoniacum*, *D. aucheri*, *D. aitchisonii*, *D. glabrum*),

Table 3 Volatile compounds identified in *Dorema* species

Dorema species	Origin in Iran	Analyzed plant part	Stage/ harvesting month	Extraction type	Yield (%)	Major compounds (%)	References
D. ammoniacum	Abadeh	S	Se.S	HD	0.5 (w/w)	Hexadecanal (11.1), α-cadinol (6.6), sesquicineol-2-one (6.6)	Hosseini et al. (2014)
		Se	Se.S	HD	0.3 (w/w)	2-Pentadecanone (19.1), β-eudesmol (17.2), germacrene D (5.8)	Hosseini et al. (2014)
	Fereydunshahr	AP	March, Fl.S	HD	0.31 (v/w)	Limonene (49.18), neophytadiene (10.21), β-caryophyllene (3.54)	Zandpour et al. (2016)
	Semnan	F	Fl.S	HD	0.09 (w/w)	(*Z*)-Ocimenone (22.3), (*E*)-ocimenone (18.1), β-cyclocitral (9.9)	Yousefzadi et al. (2011) Yousefzadi et al. (2009)
	Shahroud	S	July	HD	0.3 (w/w)	α-Muurolol (13.68), (*E*)-nerolidol (5.09), β-caryophyllene (4.39)	Masoudi and Kakavand (2017)
		L	July	HD	0.7 (w/w)	(*E*)-β-Ocimene (30.94), *p*-cymene (10.03), (*Z*)-β-ocimene (7.11)	Masoudi and Kakavand (2017)
D. aucheri	Damaneh	L	Before Fl.S	HD	0.4 (v/w)	β-Caryophyllene (35.73 ± 2.0), thymol (26.84 ± 0.9), caryophyllene oxide (6.3 ± 0.2)	Akbarian et al. (2016)
	Dishmook	L	Before Fl.S	HD	0.28 (v/w)	Caryophyllene oxide (29.98 ± 0.02), thymol (29.64 ± 1.0), β-caryophyllene (7.17 ± 0.02)	Akbarian et al. (2016)
	Fereydunshahr	L	Before Fl.S	HD	0.57 (v/w)	β-Caryophyllene (34.23 ± 3.0), thymol (25.96 ± 1.0), caryophyllene oxide (6.85 ± 0.15)	Akbarian et al. (2016)
	Gorgue	L	Before Fl.S	HD	0.68 (v/w)	β-Caryophyllene (32.45 ± 2.0), thymol (23.45 ± 2.1), caryophyllene oxide (8.24 ± 0.16)	Akbarian et al. (2016)
	Hezar mountain	AP	June	HD	0.16 (w/w)	α-Eudesmol (31.2), δ-cadinene (10.9), 2-pentadecanone (5.9)	Masoudi et al. (2006)
	Margoon	L	Before Fl.S	HD	0.49 (v/w)	β-Caryophyllene (27.56 ± 1.0), thymol (27.23 ± 1.0), caryophyllene oxide (12.89 ± 0.06)	Akbarian et al. (2016)
	Oramanat	L	May	Nd	Nd	Curzerene (18.7), spathulenol (6.68), isohibaene (6.16)	Khanahmadi et al. (2012)
D. glabrum	Ghaflankuh	R	June	HD	0.3 (v/w)	Myristicin (14.1), elemicin (11.7), α-cedrene (7.7)	Delnavazi et al. (2015a)

AP aerial parts, *F* flowers, *Fl.S* flowering stage, *HD* hydrodistillation, *L* leaves, *Nd* not determined, *R* roots, *S* stems, *Se* seeds, *Se.S* seeding stage

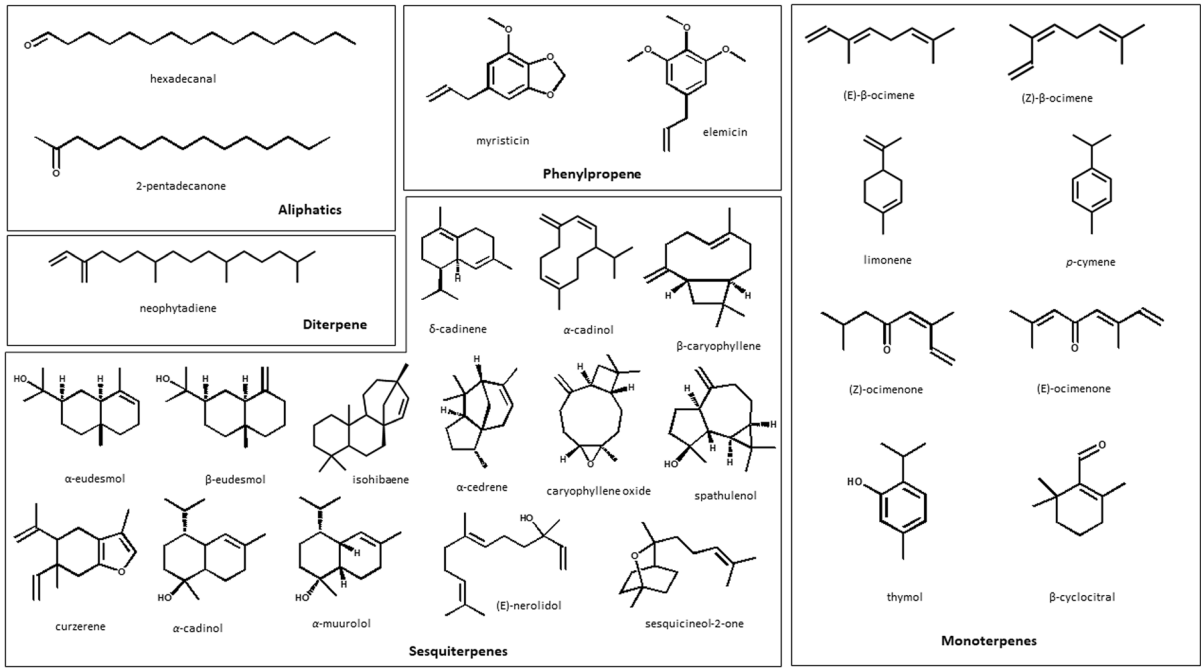

Fig. 2 Chemical structures of the main essential oil compounds from *Dorema* species

antimicrobial (*D. ammoniacum*, *D. aucheri*), and neuroprotective (*D. ammoniacum*) activities were reported. In the assays, methanolic or hydroethanolic extracts of aerial parts were mostly used, along with oleo gum resin in case of *D. ammoniacum*. In most cases, studies were performed using crude extracts without identifying the compounds responsible for bioactivity and determining their mechanisms of action, bioavailability, pharmacokinetics and physiological pathways. Therefore, detailed investigations are still needed regarding both the chemical characterization and the explanation of the results from preclinical experiments, including possible toxicity, as well as the standardization of formulations based on *Dorema* species ingredients.

Analgesic activity

Different doses (125, 250, 500 mg/kg) of aqueous solution of *D. ammoniacum* resin were examined for their analgesic activity in male albino mice. The sample was effective in a dose-dependent manner ($P < 0.05$) both in acute and chronic phase of formalin test as well as in acetic acid writing test 30 min after its injection. In particular, the dose of 500 mg/kg significantly reduced the pain ($p < 0.001$) (Bakhtiarian et al. 2017).

Anticonvulsant activity

The anticonvulsant potential of *D. ammoniacum* resin was analyzed by inducing seizures in mice with pentylenetetrazole (60 mg/kg). In comparison to Diazepam (1 mg/kg) used as a control and able of providing 100% protection, the resin (700 and 1000 mg/kg) revealed weak protection by 33% (Motevalian et al. 2017).

Antidiabetic activity

The ethanolic (EtOH) extract (30%) of *D. aucheri* leaves was studied for its effect on blood glucose and insulin levels in nicotinamide/streptozotocin-induced diabetic adult male Wistar rats. After a daily administartion of 100, 200 and 400 mg/kg for 4 weeks, the insulin level significantly increased (up to 30.071 ± 1.92 µLU/mL) and blood glucose concentration decreased (up to 121.429 ± 9.13 mg/dl) in treated mice compared to the diabetic control group (11.916 ± 1.21 µLU/mL and 167.5 ± 8.60,

Table 4 Biological activities of *Dorema* species

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/model	References
Analgesic	*D. ammoniacum*	Aqueous ex. of gum	T: 90 min (at 125 mg/kg, in acute phase) T: 78 min (at 250 mg/kg, in acute phase) T: 75 min (at 500 mg/kg, in acute phase) T: 70 min (at 125 mg/kg, in chronic phase) T: 55 min (at 250 mg/kg, in chronic phase) T: 52 min (at 500 mg/kg, in chronic phase)	Formalin	Morphine Aspirin morphine aspirin	T: 45 min (in acute phase) T: 65 min (in acute phase) T: 35 min (in chronic phase) T: 50 min (in chronic phase)	Mice (in vivo)	Bakhtiarian et al. (2017)
Anticonvulsant	*D. ammoniacum*	Gum	P: 33% after 30 min (at 700 mg/kg) P: 33% after 30 min (at 1000 mg/kg)	Pentylenetetrazol (PTZ) induced seizure	Diazepam (1 mg/kg)	P: 100% after 30 min (at 1 mg/kg)	Mice (in vivo)	Motevalian et al. (2017)
Antidiabetic	*D. aucheri*	EtOH ex. (30%) of L	FBGL: 121.429 ± 9.13 mg/dL (at 100 mg/kg) FBGL: 128.5 ± 3.46 mg/dL (at 200 mg/kg) FBGL: 122.375 ± 5.61 mg/dL (at 400 mg/kg) IL: 25.857 ± 1.63 µLU/mL (at 100 mg/kg) IL: 30.071 ± 1.92 µLU/mL (at 200 mg/kg) IL: 24.9 ± 3.89 µLU/mL (at 400 mg/kg)	Nicotinamide/ streptozotocin-induction	Glibenclamide (0.25 mg/kg)	FBGL: 110.5 ± 5.13 mg/dL IL: 19.071 ± 1.76 µLU/mL	Wistar rats (in vivo)	Ahangarpour et al. (2014)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/model	References
Anti-inflammatory	*D. ammoniacum*	Aqueous ex. of gum	PE: 3.1 mm (at 125 mg/kg after 1 h) PE: 3.6 mm (at 250 mg/kg after 1 h) PE: 2.4 mm (at 500 mg/kg after 1 h) PE: 3.4 mm (at 125 mg/kg after 2 h) PE: 3.8 mm (at 250 mg/kg after 2 h) PE: 2.5 mm (at 500 mg/kg after 2 h) PE: 3.2 mm (at 125 mg/kg after 3 h) PE: 3.7 mm (at 250 mg/kg after 3 h) PE: 2.5 mm (at 500 mg/kg after 3 h) PE: 3.2 mm (at 125 mg/kg after 4 h) PE: 3.6 mm (at 250 mg/kg after 4 h) PE: 2.5 mm (at 500 mg/kg after 4 h) PE: 3.3 mm (at 125 mg/kg after 5 h) PE: 3.5 mm (at 250 mg/kg after 5 h) PE: 2.4 mm (at 500 mg/kg after 5 h)	Carrageenan-induced paw edema	Indomethacin (500 mg/kg)	PE: 2.3 mm (after 1 h) PE: 2.2 mm (after 2 h) PE: 2.1 mm (after 3 h) PE: 2.2 mm (after 4 h) PE: 2.1 mm (after 5 h)	Mice (in vivo)	Bakhtiarian et al. (2017)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ |strain/ model	References
	D. ammoniacum	Aqueous ex. of gum	PE: 0.14 ± 0.02 cm^3; I%: 54.14 (at 100 mg/kg − 30 min) PE: 0.09 ± 0.03 cm^3; I%: 69.61 (at 200 mg/kg − 30 min) PE: 0.11 ± 0.02 cm^3; I%: 65.19 (at 300 mg/kg − 30 min) PE: 0.10 ± 0.02 cm^3; I%: 66.48 (at 100 mg/kg − 1 h) PE: 0.04 ± 0.02 cm^3; I%: 88.27 (at 200 mg/kg − 1 h) PE: 0.06 ± 0.01 cm^3; I%: 80.45 (at 300 mg/kg − 1 h) PE: 0.01 ± 0.00 cm^3; I%: 98.85 (at 100 mg/kg − 2 h) PE: 0.01 ± 0.01 cm^3; I%: 96.55 (at 200 mg/kg − 2 h) PE: 0.05 ± 0.02 cm^3; I%: 83.91 (at 300 mg/kg − 2 h) PE: 0.01 ± 0.00 cm^3; I%: 98.45 (at 100 mg/kg − 3 h) PE: 0.01 ± 0.00 cm^3; I%: 96.90 (at 200 mg/kg − 3 h) PE: 0.05 ± 0.03 cm^3; I%: 76.74 (at 300 mg/kg − 3 h) PE: 0.01 ± 0.00 cm^3; I%: 98.45 (at 100 mg/kg − 4 h) PE: 0.01 ± 0.00 cm^3; I%: 98.45 (at 200 mg/kg − 4 h) PE: 0.02 ± 0.01 cm^3; I%: 91.47 (at 300 mg/kg − 4 h) PE: 0.23 ± 0.01 cm^3; I%: 15.3 (at 100 mg/kg − 30 min) PE: 0.11 ± 0.01 cm^3; I%: 59.85 (at 100 mg/kg − 1 h) PE: 0.21 ± 0.08 cm^3; I%: 19.5 (at 100 mg/kg − 2 h) PE: 0.16 ± 0.02 cm^3; I%: 42.25 (at 100 mg/kg − 3 h) PE: 0.16 ± 0.02 cm^3; I%: 43.26 (at 100 mg/kg − 4 h)	Carrageenan-induced paw edema	Mefenamic acid (30 mg/kg) Diclofenac gel (2%) topical application	PE: 0.11 ± 0.02 cm^3; I%: 62.43 (30 min) PE: 0.11 ± 0.03 cm^3; I%: 63.69 (1 h) PE: 0.10 ± 0.02 cm^3; I%: 67.24 (2 h) PE: 0.08 ± 0.02 cm^3; I%: 62.79 (3 h) PE: 0.04 ± 0.01 cm^3; I%: 82.17 (4 h) PE: 0.23 ± 0.05 cm^3; I%: 14.6 (30 min) PE: 0.31 ± 0.03 cm^3; I%: -14.6 (1 h) PE: 0.22 ± 0.03 cm^3; I%: 18.0 (2 h) PE: 0.21 ± 0.02 cm^3; I%: 26.76 (3 h) PE: 0.21 ± 0.02 cm^3; I%: 26.24 (4 h)	Wistar rats (in vivo)	Pandpazir et al. (2018)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ lstrain/ model	References
	D. kopetdaghense	Kopetdaghin A (**24**) Kopetdaghin C (**26**) Kopetdaghin E (**28**)	I%: 57.30 ± 0.66 (at 10 μg/mL) I%: 77.81 ± 0.16 (at 20 μg/mL) I%: 94.20 ± 0.38 (at 50 μg/mL) I%: 100 (at 100 μg/mL) I%: 14.97 ± 0.32 (at 10 μg/mL) I%: 43.68 ± 0.28 (at 20 μg/mL) I%: 75.75 ± 0.12 (at 50 μg/mL) I%: 100 (at 100 μg/mL) I%: 43.59 ± 0.24 (at 10 μg/mL) I%: 63.09 ± 0.10 (at 20 μg/mL) I%: 75.37 ± 0.11 (at 50 μg/mL) I%: 100 (at 100 μg/mL)	MTT	Nd	Nd	J774A.1 murine macrophage (in vitro)	Rabe et al. (2015) Zandpour et al. (2018)
Antimicrobial	*D. aucheri*	MeOH (95%) ex. of AP	IZ: 8.79 ± 0.53 mm IZ: 7.76 ± 0.31 mm IZ: 10.32 ± 0.84 mm IZ: 12.14 ± 0.96 mm IZ: 12.35 ± 1.27 mm IZ: 12.11 ± 1.22 mm IZ: 14.3 ± 1.36 mm IZ: 12.6 ± 0.84 mm IZ: 8.48 ± 0.58 mm I: 90.9 ± 3.58% I: 80.6 ± 2.32% I: 93.6 ± 1.14% I: 97.9 ± 2.12% I: 97.5 ± 1.64% I: 97.9 ± 1.42% I: 99.1 ± 0.76% I: 93 ± 1.08%	DD MbD	Nd Nd	Nd Nd	*Staphylococcus aureus* (ATCC-25,923) *Bacillus subtilis* (ATCC-15,561) *B. cereus* (ATCC-14,579) *Listeria monocytogenes* (ATCC-19,115) *Escherichia coli* O157 (H7 ATCC-43,895) *Citrobacter freundii* (ATCC-43,864) *Salmonella enteritidis* (ATCC-13,076)	Gheisari et al. (2016)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			I: 88 ± 2.26%				*Enterococcus aerogenes* (ATCC-13,048)	
							Klebsiella pneumoniae (ATCC-3583)	
							Staphylococcus aureus (ATCC-25,923)	
							Bacillus subtilis (ATCC-15,561)	
							B. cereus (ATCC-14,579)	
							Listeria monocytogenes (ATCC-19,115)	
							Escherichia coli O157 (H7 ATCC-43,895)	
							Citrobacter freundii (ATCC-43,864)	
							Salmonella enteritidis (ATCC-13,076)	
							Enterococcus aerogenes (ATCC-13,048)	
							Klebsiella pneumoniae (ATCC-3583)	
	D. aucheri	$CHCl_3$ ex. of R	MIC: 0.62 µg/mL	MbD	Ciprofloxacin	MIC: 0.15 µg/mL	*E. coli*	Khan et al. (2014)
		n-Hexane ex. of R	MIC: 2.50 µg/mL			MIC: 0.62 µg/mL	*B. subtilis*	
			MIC: 0.31 µg/mL			MIC: 0.15 µg/mL	*S. aureus*	
			MIC: 0.15 µg/mL			MIC: 0.31 µg/mL	*Shigella flexneri*	
			MIC: 0.15 µg/mL				*E. coli*	
			MIC: 0.31 µg/mL				*B. subtilis*	
			MIC: 0.15 µg/mL				*S. aureus*	
			MIC: 0.31 µg/mL				*Shigella flexneri*	
	D. aucheri	MeOH (80%) ex. of L	MIC: 10 mg/mL	MbD	Nd	Nd	*S. aureus* (PTCC-11,778)	Mianabadi et al. (2015)
		MeOH (80%) ex. of S	MIC: 20 mg/mL					

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
		MeOH (80%) ex. of Fl	No activity				*B. cereus* (PTCC-1112)	
			MIC: 40 mg/mL				*E. coli* (PTCC-1330)	
			MIC: 20 mg/mL				*Salmonella enterica* (PTCC-1639)	
			MIC: 40 mg/mL				*S. aureus* (PTCC-11,778)	
			No activity				*B. cereus* (PTCC-1112)	
			MIC: 40 mg/mL				*E. coli* (PTCC-1330)	
			MIC: 10 mg/mL				*Salmonella enterica* (PTCC-1639)	
			MIC: 20 mg/mL				*S. aureus* (PTCC-11,778)	
			No activity				*B. cereus* (PTCC-1112)	
			MIC: 20 mg/mL				*E. coli* (PTCC-1330)	
							Salmonella enterica (PTCC-1639)	
	D. ammoniacum	DCM-MeOH (1:1) ex. of gum	Complete I (at 500 and 1000 µg/mL)	ADS	Ciprofloxacin (3 µg/mL)	Complete I	*B. cereus* var mycoides (ATCC-11,778)	Kumar et al. (2006)
			Complete I (at 500 and 1000 µg/mL)		Amphotericin-B (3 µg/mL)	Complete I	*B. pumilus* (ATCC-14,884)	
			Complete I (at 500 and 1000 µg/mL)			Complete I	*B. subtilis* (ATCC-6633)	
			Complete I (at 500 and 1000 µg/mL)			Complete I	*Bordetella bronchiseptica* (ATCC-4617)	
			Complete I (at 500 and 1000 µg/mL)			Complete I	*Micrococcus luteus* (ATCC-9341)	
			Complete I (at 500 and 1000 µg/mL)			Complete I	*S. aureus* (ATCC-29,737)	
			Complete I (at 500 and 1000 µg/mL)			Complete I	*S. epidermidis* (ATCC 12,228)	
			No I (at 500 and 1000 µg/mL)			Complete I		

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			Complete I (at 500 and 1000 µg/mL)				*E. coli* (ATCC 10,536)	
			No I (at 500 and 1000 µg/mL)				*K. pneumoniae* (ATCC-10,031)	
			Complete I (at 500 and 1000 µg/mL)				*Pseudomonas aeruginosa* (ATCC-9027)	
			Complete I (at 500 and 1000 µg/mL)				*S. faecalis* (MTCC-8043)	
			Complete I (at 500 and 1000 µg/mL)				*Saccharomyces cerevisiae* (ATCC-9763) *C. albicans* (MTCC-10,231)	
			Complete I (at 500 and 1000 µg/mL)				*Aspergillus niger* (MTCC-1344)	
	D. ammoniacum	DCM-MeOH (1:1) ex. of gum	No I (at 10 and 20 µg/mL)	ADS	Ciprofloxacin (2 µg/mL)	Complete I	*B. cereus* (ATCC 11,778)	Rajani et al. (2002)
			No I (at 10 and 20 µg/mL)			Complete I	*B. pumilus* (ATCC-14,884)	
			No I (at 10 and 20 µg/mL)			Complete I	*B. subtilis* (ATCC-6633)	
			No I (at 10 and 20 µg/mL)			Complete I	*M. luteus* (ATCC-9341)	
			No I (at 10 and 20 µg/mL)			Complete I	*S. epidermidis* (ATCC-6538)	
			No I (at 10 and 20 µg/mL)			Complete I	*S. aureus* (ATCC-29,737)	
			No I (at 10 and 20 µg/mL)			Complete I	*S. faecalis* (ATCC-8043)	
			No I (at 10 and 20 µg/mL)			Complete I	*Bordetella bronchiseptica* (ATCC-4617)	
			No I (at 10 and 20 µg/mL)			Complete I	*E. coli* (ATCC-10,536)	
			No I (at 10 and 20 µg/mL)				*K. pneumoniae* (ATCC-10,031)	
			No I (at 10 and 20 µg/mL)				*Pseudomonas aeruginosa* (ATCC-9027)	
			No I (at 10 and 20 µg/mL)				*S. cerevisiae* (ATCC-9763)	

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			No I (at 10 and 20 µg/mL)				*C. albicans* (ATCC-10,231)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*A. niger* (ATCC-16,404)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*B. cereus* (ATCC 11,778)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*B. pumilus* (ATCC-14,884)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*B. subtilis* (ATCC-6633)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*M. luteus* (ATCC-9341)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*S. epidermidis* (ATCC-6538)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*S. aureus* (ATCC-29,737)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*S. faecalis* (ATCC-8043)	
			No I (at 40, 60, 100 and 200 µg/mL)				*Bordetella bronchiseptica* (ATCC-4617)	
			No I (at 40, 60, 100 and 200 µg/mL)				*E. coli* (ATCC-10,536)	
			No I (at 40, 60, 100 and 200 µg/mL)				*K. pneumoniae* (ATCC-10,031)	
			Complete I (at 40, 60, 100 and 200 µg/mL)				*Pseudomonas aeruginosa* (ATCC-9027)	
			No I (at 40, 60, 100 and 200 µg/mL)				*S. cerevisiae* (ATCC-9763)	
			Nomplete I (at 40, 60, 100 and 200 µg/mL)				*C. albicans* (ATCC-10,231)	
							A. niger (ATCC-16,404)	
	D. ammoniacum	EO of F	IZ: 23 ± 0.2 mm	DD	Tetracycline	IZ: 21 ± 0.8 mm	*B. subtilis* (ATCC-465)	Yousefzadi et al. (2009, 2011)
			IZ: 13 ± 0.4 mm	MbD	(30 µg/disc)	IZ: 9 ± 0.4 mm		
			IZ: 17 ± 0.3 mm	DD	Gentamicin	IZ: 20 ± 0.4 mm	*E. faecalis* (ATCC-29,737)	
			IZ: 22 ± 0.8 mm	MbD	(10 µg/disc)	IZ: 34 ± 0.8 mm		
			IZ: 14 ± 0.2 mm	DD	Nystatine	No activity	*S. aureus* (ATCC-25,923)	
			IZ: 12 ± 0.4 mm	MbD	(30 µg/disc)	No activity		
			No activity			No activity	*S. epidermidis* (ATCC-12,228)	

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			No activity			Nt	*E. coli* (ATCC-25,922)	
			IZ: 10 ± 0.4 mm			Nt		
			IZ: 11 ± 0.2 mm			Nt	*K. pneumoniae* (ATCC-10,031)	
			MIC: 3.75 mg/mL			MIC: 3.2 mg/mL		
			MIC: 15 mg/mL			MIC: 6.4 mg/mL	*P. aeruginosa* (ATCC-85,327)	
			MIC: 7.5 mg/mL			MIC: 3.2 mg/mL		
			MIC: 3.75 mg/mL			MIC: 1.6 mg/mL	*A. niger* (ATCC-16,404)	
			MIC: 15 mg/mL			Nt		
			MIC: 15 mg/mL			Nt	*C. albicans* (ATCC-10,231)	
			Nt			Nt		
			Nt			Nt	*S. cerevisiae* (ATCC-9763)	
			MIC: >10 mg/mL			Nt		
			MIC: >10 mg/mL			Nt	*B. subtilis* (ATCC-465)	
						Nt		
						No activity	*E. faecalis* (ATCC-29,737)	
						No activity		
						No activity	*S. aureus* (ATCC-25,923)	
						No activity		
						IZ: 23 ± 0.8 mm	*S. epidermidis* (ATCC-12,228)	
						IZ: 20 ± 0.8 mm		
						IZ: 12 ± 0.4 mm	*E. coli* (ATCC-25,922)	
						Nt		
						Nt	*K. pneumoniae* (ATCC-10,031)	
						Nt		
						Nt	*P. aeruginosa* (ATCC-85,327)	
						Nt		
						Nt	*A. niger* (ATCC-16,404)	
						Nt		
						Nt	*C. albicans* (ATCC-10,231)	
						MIC: 3.2 mg/mL		
						MIC: 3.2 mg/mL	*S. cerevisiae* (ATCC-9763)	
						MIC: 6.4 mg/mL		
						Nt	*B. subtilis* (ATCC-465)	
						Nt		
						Nt	*E. faecalis* (ATCC-29,737)	
						Nt		
						Nt	*S. aureus* (ATCC-25,923)	
						Nt		
						Nt	*S. epidermidis* (ATCC-12,228)	
						Nt		

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
						Nt	*E. coli* (ATCC-25,922)	
						Nt		
						Nt	*K. pneumoniae* (ATCC-10,031)	
						Nt		
						IZ: 16 ± 0.4 mm	*P. aeruginosa* (ATCC-85,327)	
						IZ: 18 ± 0.4 mm	*A. niger* (ATCC-16,404)	
						IZ: 18 ± 0.8 mm		
						Nt	*C. albicans* (ATCC-10,231)	
						Nt		
						Nt	*S. cerevisiae* (ATCC-9763)	
						Nt		
						Nt	*B. subtilis* (ATCC-465)	
						Nt		
						Nt	*E. faecalis* (ATCC-29,737)	
						MIC: 6.4 mg/mL	*S. aureus* (ATCC-25,923)	
						MIC: 3.2 mg/mL		
						MIC: 1.6 mg/mL	*S. epidermidis* (ATCC-12,228)	
							E. coli (ATCC-25,922)	
							K. pneumoniae (ATCC-10,031)	
							P. aeruginosa (ATCC-85,327)	
							A. niger (ATCC-16,404)	
							C. albicans (ATCC-10,231)	
							S. cerevisiae (ATCC-9763)	
							B. subtilis (ATCC-465)	
							E. faecalis (ATCC-29,737)	
							S. aureus (ATCC-25,923)	
							S. epidermidis (ATCC-12,228)	

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
							E. coli (ATCC-25,922)	
							K. pneumoniae (ATCC-10,031)	
							P. aeruginosa (ATCC-85,327)	
							A. niger (ATCC-16,404)	
							C. albicans (ATCC-10,231)	
							S. cerevisiae (ATCC-9763)	
							B. subtilis (ATCC-465)	
							E. faecalis (ATCC-29,737)	
							S. aureus (ATCC-25,923)	
							S. epidermidis (ATCC-12,228)	
							E. coli (ATCC-25,922)	
							K. pneumoniae (ATCC-10,031)	
							P. aeruginosa (ATCC-85,327)	
							A. niger (ATCC-16,404)	
							C. albicans (ATCC-10,231)	
							S. cerevisiae (ATCC-9763)	
	D. ammoniacum	Aqueous ex. of AP	IZ: 6.4 ± 0.1 mm	DD	$AgNO_3$	IZ: 9.1 ± 0.1 mm	*E. coli* (ATCC-35,218)	Zandpour et al. (2018)
		Silver nanoparticles + aqueous AP	IZ: 6.4 ± 0.1 mm	DD		IZ: 8.0 ± 0.1 mm		
			IZ: 6.4 ± 0.1 mm	MbD		IZ: 9.0 ± 0.1 mm	*Salmonella typhimurium* (ATCC-14,028)	
			IZ: 6.4 ± 0.1 mm			IZ: 8.5 ± 0.1 mm		
			IZ: 10.7 ± 0.1 mm				*S. aureus* (ATCC-29,213)	
			IZ: 9.0 ± 0.1 mm					
			IZ: 9.2 ± 0.1 mm				*B. cereus* (ATCC-14,579)	
			IZ: 9.4 ± 0.1 mm					

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			MIC: 0.94 μg/mL				*E. coli* (ATCC-35,218)	
			MIC: 0.94 μg/mL				*Salmonella typhimurium* (ATCC-14,028)	
			MIC: 0.12 μg/mL				*S. aureus* (ATCC-29,213)	
			MIC: 0.23 μg/mL				*B. cereus* (ATCC-14,579)	
			MBC: 1.87 μg/mL				*E. coli* (ATCC-35,218)	
			MBC: 1.87 μg/mL				*Salmonella typhimurium* (ATCC-14,028)	
			MBC: 0.23 μg/mL				*S. aureus* (ATCC-29,213)	
			MBC: 0.47 μg/mL				*B. cereus* (ATCC-14,579)	
							E. coli (ATCC-35,218)	
							Salmonella typhimurium (ATCC-14,028)	
							S. aureus (ATCC-29,213)	
							B. cereus (ATCC-14,579)	
	D. ammoniacum	MeOH ex. of Se	MIC: 2.5 mg/mL	MbD	Gentamicin	MIC: ≤4 μg/mL	*E. coli 8137*	Abedini et al. (2014)
			MIC: 2.5 mg/mL		Vancomycin	MIC: ≤4 μg/mL	*E. coli 8138 (pr)*	
			MIC: 1.2 mg/mL		Amoxicillin	MIC: ≤4 μg/mL	*E. coli 8157 (pfr)*	
			MIC: 2.5 mg/mL		Amphotericin B	MIC: ≤4 μg/mL	*E. coli (ATCC-25,922)*	
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL		
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL	*Klebsiella pneumoniae 11,016*	
			MIC: 10 mg/mL			MIC: ≤4 μg/mL		
			MIC: 10 mg/mL			MIC: >8 μg/mL	*K. pneumoniae 11,017 (pr)*	
			MIC: 10 mg/mL			MIC: ≤4 μg/mL		
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL	*P. aeruginosa 8131*	
			MIC: 10 mg/mL			MIC: ≤4 μg/mL	*P. aeruginosa (ATCC-27,583)*	
			MIC: 2.5 mg/mL			MIC: >8 μg/mL		
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL		

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			MIC: 2.5 mg/mL			MIC: >8 μg/mL	*Proteus mirabilis 11,060*	
			MIC: <0.3 mg/mL			MIC: ≤4 μg/mL	*Providencia stuartii 11,038*	
			MIC: 1.2 mg/mL			MIC: ≤4 μg/mL	*Salmonella sp. 11,033*	
			MIC: 2.5 mg/mL			MIC: >8 μg/mL	*Salmonella sp. 11,037 (CMY-2)*	
			MIC: 10 mg/mL			MIC: ≤4 μg/mL	*Serratia marcescens 11,056*	
			MIC: 10 mg/mL			MIC: ≤4 μg/mL	*S. marcescens 11,057 (cr)*	
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL	*Stenotrophomonas maltophilia*	
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL	*Acinetobacter baumanii 9010 (VEB-1)*	
			MIC: 2.5 mg/mL			MIC: >8 μg/mL	*A. baumanii 9011 (multiresistant) Citrobacter freundii 11,041*	
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL	*C. freundii 11,042 (cr)*	
			MIC: 2.5 mg/mL			MIC: ≤4 μg/mL	*C. freundii 11,043 (TEM-3)*	
			MIC: <0.3 mg/mL			MIC: >8 μg/mL	*Enterobacter cloacae 11,050*	
			MIC: <0.3 mg/mL			MIC: ≤4 μg/mL	*E. cloacae 11,051 (cr)*	
			MIC: <0.3 mg/mL			MIC: ≤4 μg/mL	*E. cloacae 11,053 (NDM 1)*	
			MIC: <0.3 mg/mL			MIC: ≤4 μg/mL	*E. aerogenes 9004 (BLSE)*	
			MIC: <0.3 mg/mL			MIC: ≤4 μg/mL	*E. faecalis C159-6*	
			MIC: <0.3 mg/mL			MIC: ≤4 μg/mL	*Mycobacterium smegmatis 5003*	
			MIC: <0.3 mg/mL			MIC: ≤4 μg/mL	*S. aureus 8146 (mkr)*	
			MIC: 0.6 mg/mL			intermediate susceptibility	*S. aureus 8147*	
			MIC: 1.2 mg/mL			MIC: >8 μg/mL	*S. epidermidis 5001*	
			MIC: 0.6 mg/mL			No activity		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		
						MIC: >16 μg/mL		

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
						MIC: >16 μg/mL	*S. epidermidis 10,282*	
						MIC: >16 μg/mL		
						MIC: >16 μg/mL	*S. lugdunensis T26A3*	
						MIC: >16 μg/mL	*S. warneri T12A12*	
						MIC: >16 μg/mL	*Corynebacterium striatum T25-17*	
						MIC: >16 μg/mL		
						MIC: >16 μg/mL	*Enterococcus sp. 8152*	
						MIC: >16 μg/mL	*Enterococcus sp. 8153*	
						MIC: ≤4 μg/mL	*C. albicans 10,286*	
						MIC: >16 μg/mL	*E. coli 8137*	
						MIC: >16 μg/mL	*E. coli 8138 (pr)*	
						MIC: ≤4 μg/mL	*E. coli 8157 (pfr)*	
						MIC: ≤4 μg/mL	*E. coli (ATCC-25,922)*	
						MIC: ≤4 μg/mL	*Klebsiella pneumoniae 11,016*	
						MIC: ≤4 μg/mL		
						MIC: ≤4 μg/mL		
						MIC: >16 μg/mL	*K. pneumoniae 11,017 (pr)*	
						MIC: ≤4 μg/mL	*P. aeruginosa 8131*	
						MIC: ≤4 μg/mL	*P. aeruginosa (ATCC-27,583)*	
						MIC: ≤4 μg/mL		
						No activity	*Proteus mirabilis 11,060*	
						Intermediate susceptibility		
						MIC: >16 μg/mL	*Providencia stuartii 11,038*	
						MIC: >16 μg/mL		
						Intermediate susceptibility	*Salmonella sp. 11,033*	
						MIC: >16 μg/mL		
						MIC: >16 μg/mL	*Salmonella sp. 11,037 (CMY-2)*	
						MIC: >16 μg/mL		
						MIC: >16 μg/mL	*Serratia marcescens 11,056*	
						MIC: >16 μg/mL		
						MIC: ≤4 μg/mL	*S. marcescens 11,057 (cr)*	
						MIC: >16 μg/mL		
						MIC: >16 μg/mL	*Stenotrophomonas maltophilia*	
						MIC: >16 μg/mL		

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
						MIC: >16 µg/mL	*Acinetobacter baumanii 9010 (VEB-1)*	
						MIC: >16 µg/mL		
						MIC: >16 µg/mL	*A. baumanii 9011 (multiresistant)*	
						MIC: >16 µg/mL		
						MIC: ≤4 µg/mL	*Citrobacter freundii 11,041*	
						MIC: >16 µg/mL		
						MIC: >16 µg/mL	*C. freundii 11,042 (cr)*	
						MIC: >16 µg/mL		
						MIC: >16 µg/mL	*C. freundii 11,043 (TEM-3)*	
						MIC: >16 µg/mL		
						MIC: >16 µg/mL	*Enterobacter cloacae 11,050*	
						MIC: >16 µg/mL	*E. cloacae 11,051 (cr)*	
						MIC: ≤4 µg/mL		
						MIC: ≤4 µg/mL	*E. cloacae 11,053 (NDM 1)*	
						MIC: ≤4 µg/mL		
						MIC: ≤4 µg/mL	*E. aerogenes 9004 (BLSE)*	
						MIC: ≤4 µg/mL	*E. faecalis C159-6*	
						MIC: ≤4 µg/mL	*Mycobacterium smegmatis 5003*	
						MIC: ≤4 µg/mL		
						MIC: ≤4 µg/mL	*S. aureus 8146 (mkr)*	
						MIC: ≤4 µg/mL		
						MIC: ≤4 µg/mL	*S. aureus 8147*	
						No activity	*S. epidermidis 5001*	
						No activity		
						No activity	*S. epidermidis 10,282*	
						No activity		
						No activity	*S. lugdunensis T26A3*	
						No activity		
						No activity	*S. warneri T12A12*	
						No activity	*Corynebacterium striatum T25-17*	
						No activity		
						No activity	*Enterococcus sp. 8152*	
						No activity		
						No activity	*Enterococcus sp. 8153*	
						No activity		
						No activity	*C. albicans 10,286*	
						No activity	*E. coli 8137*	
						No activity	*E. coli 8138 (pr)*	

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
						No activity	*E. coli 8157 (pfr)*	
						No activity	*E. coli (ATCC-25,922)*	
						No activity		
						No activity	*Klebsiella pneumoniae 11,016*	
						No activity		
						No activity	*K. pneumoniae 11,017 (pr)*	
						No activity		
						No activity	*P. aeruginosa 8131*	
						No activity	*P. aeruginosa (ATCC-27,583)*	
						No activity		
						No activity	*Proteus mirabilis 11,060*	
						No activity		
						No activity	*Providencia stuartii 11,038*	
						No activity		
						No activity	*Salmonella sp. 11,033*	
						No activity		
						No activity	*Salmonella sp. 11,037 (CMY-2)*	
						No activity		
						No activity	*Serratia marcescens 11,056*	
						No activity		
						No activity	*S. marcescens 11,057 (cr)*	
						No activity		
						No activity	*Stenotrophomonas maltophilia*	
						MIC: ≤1 μg/mL	*Acinetobacter baumanii 9010 (VEB-1)*	
							A. baumanii 9011 (multiresistant) Citrobacter freundii 11,041	
							C. freundii 11,042 (cr)	
							C. freundii 11,043 (TEM-3)	
							Enterobacter cloacae 11,050	
							E. cloacae 11,051 (cr)	

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ |strain/ model	References
							E. cloacae 11,053 (NDM 1)	
							E. aerogenes 9004 (BLSE)	
							E. faecalis C159-6	
							Mycobacterium smegmatis 5003	
							S. aureus 8146 (mkr)	
							S. aureus 8147	
							S. epidermidis 5001	
							S. epidermidis 10,282	
							S. lugdunensis T26A3	
							S. warneri T12A12	
							Corynebacterium striatum T25-17	
							Enterococcus sp. 8152	
							Enterococcus sp. 8153	
							C. albicans 10,286	
							E. coli 8137	
							E. coli 8138 (pr)	
							E. coli 8157 (pfr)	
							E. coli (ATCC-25,922)	
							Klebsiella pneumoniae 11,016	
							K. pneumoniae 11,017 (pr)	
							P. aeruginosa 8131	
							P. aeruginosa (ATCC-27,583)	
							Proteus mirabilis 11,060	

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ |strain/ model	References
							Providencia stuartii 11,038	
							Salmonella sp. 11,033	
							Salmonella sp. 11,037 (CMY-2)	
							Serratia marcescens 11,056	
							S. marcescens 11,057 (cr)	
							Stenotrophomonas maltophilia	
							Acinetobacter baumanii 9010 (VEB-1)	
							A. baumanii 9011 (multiresistant) Citrobacter freundii 11,041	
							C. freundii 11,042 (cr)	
							C. freundii 11,043 (TEM-3)	
							Enterobacter cloacae 11,050	
							E. cloacae 11,051 (cr)	
							E. cloacae 11,053 (NDM 1)	
							E. aerogenes 9004 (BLSE)	
							E. faecalis C159-6	
							Mycobacterium smegmatis 5003	
							S. aureus 8146 (mkr)	
							S. aureus 8147	
							S. epidermidis 5001	
							S. epidermidis 10,282	

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
							S. lugdunensis T26A3	
							S. warneri T12A12	
							Corynebacterium striatum T25-17	
							Enterococcus sp. 8152	
							Enterococcus sp. 8153	
							C. albicans 10,286	
Antioxidant	*D. aitchisonii*	EtOH ex. of AP	IC_{50}: 488.1 ± 18 µg/mL	DPPH	Ascorbic acid	IC_{50}: 5.05 ± 0.1 µg/mL	In vitro	Nabavi et al. (2012)
			IC_{50}: 778.2 ± 22 µg/mL	ICA	Quercetin	IC_{50}: 5.28 ± 0.2 µg/mL		
			IC_{50}: 1.3 ± 0.01 mg/mL	NOSA	BHA	IC_{50}: 53.96 ± 3.1 µg/mL		
			IC_{50}: 210.6 ± 11 µg/mL	HPSA	EDTA	IC_{50}: 18 ± 1.5 µg/mL		
					Quercetin	IC_{50}: 20 ± 1 µg/mL		
					vitamin C	IC_{50}: 21.4 ± 1.1 µg/mL		
					Quercetin	IC_{50}: 52 ± 2.6 µg/mL		
	D. aucheri	$CHCl_3$ ex. of R	IC_{50}: 132.4 ± 0.74 µg/mL	DPPH	*n*-Propyl gallate	IC_{50}: 40.8 ± 0.17 µg/mL	In vitro	Khan et al. (2014)
		n-Hexane ex. of R	IC_{50}: 104.3 ± 1.10 µg/mL		*t*-BHA	IC_{50}: 59.8 ± 0.43 µg/mL		
		MeOH ex. of L	1.7 mmol Fe^{2+}/g	FRAP	Nd	Nd	In vitro	Mianabadi et al. (2015)
		MeOH ex. of S	4.33 mmol Fe^{2+}/g	BCB				
		MeOH ex. of Fl	4.22 mmol Fe^{2+}/g					
		MeOH ex. of L	1.7 mmol Fe^{2+}/g					
		MeOH ex. of S	4.2 mmol Fe^{2+}/g					
		MeOH ex. of Fl	4.3 mmol Fe^{2+}/g					
	D. glabrum	Crude ex. of AP	IC_{50}: 68.2 ± 4.1 µg/mL	DPPH	BHT	IC_{50}: 19.5 ± 2.8 µg/mL	In vitro	Delnavazi et al. (2015b)
		PET ex. of AP	IC_{50}: 123.1 ± 7.0 µg/mL					
		$CHCl_3$ ex. of AP	IC_{50}: 94.5 ± 5.2 µg/mL					
		EtOAc ex. of AP	IC_{50}: 71.8 ± 2.8 µg/mL					
		MeOH ex. of AP	IC_{50}: 48.3 ± 4.7 µg/mL					
		Daucosterol (**40**)	IC_{50}: 224.1 ± 8.2 µg/mL					
		Chlorogenic acid (**34**)	IC_{50}: 2.23 ± 0.6 µg/mL					
		Cynarine (**39**) and 3,5-di-*O*-caffeoylquinic acid (**37**)	IC_{50}: 2.61 ± 0.4 µg/mL					
			IC_{50}: 40.6 ± 3.2 µg/mL					
		Isorhamnetin-3-*O*-β-*D*-glucopyranoside (**10**)	IC_{50}: 24.6 ± 3.1 µg/mL					
			IC_{50}: 43.2 ± 4.2 µg/mL					

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
		Isoquercetin (**11**)						
		Astragalin (**12**)						
Antiplasmodial	*D. hyrcanum*	EtOAc ex. of R	I: 73 ± 0.5% (at 10 mg/ Kg)	Peters′ 4-day suppressive	Chloroquine	I: 100 ± 4.6%	*Plasmodium berghei* (in vivo)/mice	Naghibi et al. (2015)
		4-Methoxy-6-hydroxyacetophenone-	I: 10.1 ± 9.6% (at 10 mg/Kg)	Parasite lactate dehydrogenase	(20 mg/kg)	Nd	*Plasmodium falciparum* in vitro)	
		2-*O*-β-D-gentiobioside (**22**)	I: 68.1 ± 2.5% (at 10 mg/Kg)		chloroquine diphosphate, artemisinin		chloroquine-resistant strain	
		Naghibione (**29**)	I: 29.3 ± 0.5% (at 10 mg/Kg)					
		2,3-Dihydro-7-methoxy-2S*,3R*-dimethyl-2-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c]-coumarin (**7**)	I: 23.3 ± 0.5% (at 10 mg/Kg)					
		2,3-Dihydro-7-methoxy-2R*,3R*dimethyl-2-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c]-oumarin (**9**)	IC_{50}: 28.64 µg/mL					
		MeOH ex. of R	IC_{50}: 9.79 µg/mL					
Anti-proliferative & cytotoxicity	*D. aucheri*	EtOH ex. of edible part	CZ: 152.92 ± 97.7 mm (at 200 mg/kg, 12th week)	Hematoxylin eosin	Control group (unhealthy rats)	CZ: 98.5 ± 32.5 mm (at 1st week)	Breast cancer cell/ Rat/in vivo	Gourabi et al. (2015)
			CZ: 444.146 ± 313.73 mm (at 400 mg/kg, 12th week)			CZ: 746.2 ± 379.2 mm (at 12th week)		
		PET ex. of AP	IC_{50}: 95.38 ± 2.96 µg/ mL	MTT	Nd	Nd	MDA-MB-231 (breast cancer)	Eftekhari et al. (2019)
		$CHCl_3$ ex. of AP	IC_{50}: >200 µg/mL				A549 (lung carcinoma)	
		EtOAc ex. of AP	IC_{50}: 198.53 ± 1.46 µg/ mL				HT-29 (colon carcinoma)	
		MeOH ex. of AP	IC_{50}: 117.66 ± 3.01 µg/ mL				HeLa (Cervical cancer)	
		Pickle ex.	IC_{50}: 17.00 ± 2.30 µg/ mL				Normal fibroblast cell line	
			IC_{50}: 69.7 ± 2.99 µg/mL				MDA-MB-231 (breast cancer)	
			IC_{50}: 147.66 ± 0.23 µg/ mL				A549 (lung carcinoma)	
			IC_{50}: 155.68 ± 5.50 µg/ mL				HT-29 (colon carcinoma)	
			IC_{50}: 145.38 ± 0.10 µg/ mL				HeLa (Cervical cancer)	
			IC_{50}: 48.84 ± 1.24 µg/ mL					

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			IC_{50}: >200 μg/mL				Normal fibroblast cell line	
			IC_{50}: >200 μg/mL				MDA-MB-231 (breast cancer)	
			IC_{50}: >200 μg/mL				A549 (lung carcinoma)	
			IC_{50}: >200 μg/mL				HT-29 (colon carcinoma)	
			IC_{50}: >200 μg/mL				HeLa (Cervical cancer)	
			IC_{50}: 177.41 ± 2.63 μg/mL				Normal fibroblast cell line	
			IC_{50}: >200 μg/mL				MDA-MB-231 (breast cancer)	
			IC_{50}: >200 μg/mL				A549 (lung carcinoma)	
			IC_{50}: >200 μg/mL				HT-29 (colon carcinoma)	
			IC_{50}: >200 μg/mL				HeLa (Cervical cancer)	
			IC_{50}: >200 μg/mL				Normal fibroblast cell line	
			IC_{50}: 171.27 ± 1.9 μg/mL				MDA-MB-231 (breast cancer)	
			IC_{50}: >200 μg/mL				A549 (lung carcinoma)	
			IC_{50}: >200 μg/mL				HT-29 (colon carcinoma)	
			IC_{50}: >200 μg/mL				HeLa (Cervical cancer)	
							Normal fibroblast cell line	
	D. glabrum	MeOH ex. of roots	Echisoside (**19**)	MTT	Na	Na	Adenocarcinoma gastric cell line	Jafari et al. (2018)
			Pleoside (**20**)					
			Chlorogenic acid (**34**)					
			4,5-Di-O-caffeoylquinic acid (**36**)					
			Cynarine (**39**)					
	D. hyrcanum	EtOAc ex. of R	IC_{50}: 69.67 μg/mL	MTT	Tamoxifen	IC_{50}: 4.76 μg/mL	MDBK cell line	Naghibi et al. (2015)
		Naghibione (**29**)	IC_{50}: >100 μg/mL					

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
Antithyroid	*D. aucheri*	EtOH ex. (50%) of AP	C of T_3 hormone: 0.74 ± 0.1 /L (at 100 mg/kg) C of T_3 hormone: 0.74 ± 0.37 /L (at 200 mg/kg) C of T_3 hormone: 0.63 ± 0.28 /L (at 400 mg/kg) C of T_4 hormone: 2.6 ± 0.87 /L (at 100 mg/kg) C of T_4 hormone: 2.97 ± 0.57 /L (at 200 mg/kg) C of T_4 hormone: 2.61 ± 0.26 /L (at 400 mg/kg) C of TSH: 11.63 ± 6.7 /L (at 100 mg/kg) C of TSH: 3.05 ± 3.38 /L (at 200 mg/kg) C of TSH: 1.7 ± 0.64 /L (at 400 mg/kg)	ELISA test	Control group	C of T_3 hormone: 0.52 ± 0.11 /L C of T_4 hormone: 2.46 ± 0.65 /L C of TSH hormone: 0.84 ± 0.93 /L	Wistar rat/in vivo	Azarneushan et al. (2010)
Hepatotoxicity	*D. aucheri*	EtOH ex. of L (0.4 mL/kg) EtOH ex. of L (0.8 mL/kg) EtOH ex. of L (1.6 mL/kg) EtOH ex. of L (3.2 mL/kg)	SGPT: 179.89 ± 0.14 IU/L SGOT: 93.60 ± 0.85 IU/L ALP: 189.09 ± 0.52 IU/L SGPT: 204.54 ± 0.84 IU/L SGOT: 102.67 ± 0.86 IU/L ALP: 195 ± 0.71 IU/L SGPT: 230.43 ± 1.3 IU/L SGOT: 115.89 ± 0.39 IU/L ALP: 212 ± 0.81 IU/L SGPT: 263.5 ± 1.8 IU/L	Nd	Control group (not injected)	SGPT: 86.43 ± 0.23 IU/L SGOT: 37.81 ± 0.34 IU/L ALP: 181.43 ± 0.61 IU/L	Mice/in vivo	Mostafavi et al. (2013)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			SGOT: 131.51 ± 0.2 IU/L ALP: 295.44 ± 0.99 IU/L					
	D. aucheri	EtOH (30%) ex. of L (100 mg/kg) + diabetic EtOH (30%) ex. of L (200 mg/kg) + diabetic EtOH (30%) ex. of L (400 mg/kg) + diabetic	SGPT: 54.57 ± 7.65 ng/dL SGOT: 105.62 ± 2.39 ng/dL ALP: 123.87 ± 2.13 ng/dL SGPT: 37.71 ± 2.74 ng/dL SGOT: 86.62 ± 2.47 ng/dL ALP: 112 ± 3.53 ng/dL SGPT: 48.12 ± 6.01 ng/dL SGOT: 110.75 ± 5.96 ng/dL ALP: 130.62 ± 5.04 ng/dL		Control Diabetic Diabetic + GLB (0.25 mg/kg)	SGPT: 56.25 ± 9.24 ng/dL SGOT: 87 ± 4.34 ng/dL ALP: 117.12 ± 4.50 ng/dL SGPT: 67 ± 11.40 ng/dL SGOT: 126.62 ± 11 ng/dL ALP: 139.25 ± 3.80 ng/dL SGPT: 39.83 ± 4.08 ng/dL SGOT: 101.5 ± 6.10 ng/dL ALP: 120.37 ± 3.74 ng/dL	Wistar rat/in vivo nicotinamide/ streptozotocin-induced diabetic rats	Ahangarpour et al. (2014)
Hypolipidemic	*D. aucheri*	EtOH (30%) ex. of L (100 mg/kg) + diabetic EtOH (30%) ex. of L (200 mg/kg) + diabetic EtOH (30%) ex. of L (400 mg/kg) + diabetic	TC: 57 ± 3.72 mg/dL Tr: 66.71 ± 4.15 mg/dL HDL: 47.71 ± 2.37 mg/dL VLDL: 13.34 ± 0.83 mg/dL LDL: 3.71 ± 1.63 mg/dL Leptin: 0.93 ± 0.42 ng/dL TC: 61.28 ± 3.35 mg/dL Tr: 95.42 ± 7.28 mg/dL HDL: 59 ± 2.64 mg/dL VLDL: 19.08 ± 1.45 mg/dL LDL: 1.1 ± 0.56 mg/dL Leptin: 1.49 ± 0.80 ng/dL TC: 62.62 ± 3.72 mg/dL Tr: 104 ± 9.12 mg/dL		Control Diabetic Diabetic + GLB (0.25 mg/kg)	TC: 58.625 ± 3.94 mg/dL T: 91.25 ± 10.04 mg/dL HDL: 55.37 ± 4.64 mg/dL VLDL: 18.25 ± 2 mg/dL LDL: 2.387 ± 1.09 mg/dL Leptin: 1.33 ± 0.08 ng/dL TC: 67.87 ± 1.99 mg/dL T: 126.12 ± 13.04 mg/dL HDL: 47 ± 1.70 mg/dL VLDL: 25.22 ± 2.6 mg/dL LDL: 8.8 ± 1.58 mg/dL Leptin: 1 ± 0.0 ng/dL TC: 62.66 ± 4.87 mg/dL T: 116 ± 12.54 mg/dL HDL: 49.66 ± 2.38 mg/dL VLDL: 23.2 ± 2.5 mg/dL LDL: 3.983 ± 2.75 mg/dL Leptin: 1.12 ± 0.87 ng/dL	Wistar rat/in vivo nicotinamide/ streptozotocin-induced diabetic rats	Ahangarpour et al. (2014)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			HDL: 46.625 ± 3.60 mg/dL VLDL: 20.8 ± 1.82 mg/dL LDL: 5.6 ± 2.15 mg/dL Leptin: 1.16 ± 0.13 ng/dL					
Neuroprotective	*D. ammoniacum*	Gum	RMP: -32.91 ± 0.19 mV PTZ + 0.01% gum (electrophysiological properties of F1 neuron) RMP: -37.47 ± 0.23 mV PTZ + 0.1% gum (electrophysiological properties of F1 neuron) RMP: -39.16 ± 0.11 mV PTZ + 0.3% gum (electrophysiological properties of F1 neuron) FF: 3.393 ± 0.05 Hz PTZ + 0.01% gum (electrophysiological properties of F1 neuron) FF: 2.985 ± 0.062 Hz PTZ + 0.1% gum (electrophysiological properties of F1 neuron) FF: 3.47 ± 0.04 Hz PTZ + 0.3% gum (electrophysiological properties of F1 neuron) AHP-A: -1.263 ± 0.07 mV PTZ + 0.1% gum (electrophysiological properties of F1 neuron)	Intracellular recording	Phenobarbital (600 μM)	RMP: -45.30 ± 0.25 mV RMP: -43.29 ± 0.43 mV + PTZ FF: 2.02 ± 0.05 Hz FF: 2.82 ± 0.072 Hz + PTZ AHP-A: -6.375 ± 0.15 mV AHP-A: -3.204 ± 0.162 mV + PTZ	F1 neuron of *Helix aspersa* (Iranian garden snail)/ in vivo (Epileptic activity)	Ghasemi et al. (2018)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
			AHP-A: -1.122 ± 0.06 mV PTZ + 0.3% gum (electrophysiological properties of F1 neuron)					
			RMP: -41.10 ± 0.14 mV PTZ + 0.1% gum (prophylactic effects of gum)					
			RMP: -41.37 ± 0.2 mV PTZ + 0.3% gum (prophylactic effects of gum)					
			FF: 3.155 ± 0.02 Hz 0.1% gum (prophylactic effects of gum)					
			FF: 3.04 ± 0.03 Hz 0.3% gum (prophylactic effects of gum)					
			FF: 4.64 ± 0.061 HzPTZ + 0.1% gum (prophylactic effects of gum)					
			AHP-A: (-4.567 ± 0.112 mV 0.1% gum (prophylactic effects of gum)					
			AHP-A: -2.989 ± 0.09 mV 0.3% gum (prophylactic effects of gum)					
			AHP-A: -1.714 ± 0.06 mV PTZ + 0.1% gum (prophylactic effects of gum)					
			AHP-A: -0.908 ± 0.03 mV PTZ + 0.3% gum (prophylactic effects of gum)					

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ Istrain/ model	References
	D. ammoniacum	DCM ex. of gum (2′S,5′S)-2′-Ethenyl-5′-(3-hydroxy-6-methyl-4-oxohept-5-en-2-yl)-7-methoxy-2′-methyl-4H-spiro[chromene-3,1′-cyclopentane]-2,4-dione (**1**) Doremone A (**2**) Dshamirone (**42**) Ammoresinol (**5**)	IC_{50}: 668.00 ± 17.80 µg/mL IC_{50}: 77.14 ± 3.75 µg/mL IC_{50}: 100.82 ± 5.14 µg/mL IC_{50}: 8.36 ± 0.41 µg/mL IC_{50}: 76.84 ± 3.86 µg/mL	Ellman	Physostigmine	IC_{50}: 0.80 ± 0.04 µg/mL	AChE enzyme inhibitory	Vani et al. (2019)
	D. ammoniacum	*n*-Hexane ex. of gum $CHCl_3$ ex. of gum DCM ex. of gum EtOAC ex. of gum	IC_{50}: 32.34 ± 1.25 µg/mL IC_{50}: 43.50 ± 1.52 µg/mL IC_{50}: 128.80 ± 1.25 µg/mL IC_{50}: 152.40 ± 6.12 µg/mL	Ellman	Galantamine	IC_{50}: 2.50 ± 0.20 µg/mL	AChE enzyme inhibitory	Sepahi et al. (2015)

Table 4 continued

Activity	Species	Assayed extract/plant product/compound	Measure of activity	Assay	Positive control	Activity of control	Cell lines/ strain/ model	References
Vascular toxicity	*D. ammoniacum*	EtOH (20%) ex. of gum	VA: 59.54 ± 1.34% (at 50 mg/kg) TVL: 8554.55 ± 2.40 pixel (at 50 mg/kg) VB: 127 ± 3.89 (at 50 mg/kg) Lacunarity: 0.33 ± 0.17 (at 50 mg/kg) VA: 39.22 ± 1.75% (at 100 mg/kg) TVL: 4722.84 ± 2.58 pixel (at 100 mg/kg) VB: 48 ± 3.69 (at 100 mg/kg) Lacunarity: 0.91 ± 0.43 (at 100 mg/kg)	Chicken embryo membrane	Control group	VA: 63.3 ± 1.21% TVL: 8721.32 ± 2.22pixel VB: 132 ± 4.43 Lacunarity: 0.33 ± 0.05	Fertile chicken (Ross 308) eggs	Tavakkoli et al. (2020)

AChE acetylcholinesterase, *ADS* agar dilution-streak, *AHP-A* after hyperpolarization amplitude, *ALP* alkaline phosphatase, *AP* aerial parts, *BCB* β-carotene bleaching, *BHT* butylated hydroxytoluene, *Cr* cephalosporin resistance, *CZ* cell size, *DCM* dichloromethane, *DD* Disc diffusion, *DPPH* 2,2-diphenyl-1-picrylhydrazyl, *ex.* extract, *F* fruits, *FBGL* Fasting blood glucose level, *FF* firing frequency, *Fl* flowers, *FRAP* ferric reducing antioxidant power, *GLB* glibenclamide, *HDL* high-density lipoprotein, *HPSA* hydrogen peroxide scavenging activity, *ICA* iron chelating activity, *IL* Insulin level, *IZ* Inhibition zone, *L* leaves, *LDL* low-density lipoprotein, *MBC* minimum bactericidal concentrations, *MbD* Microtiter broth dilution, *MDBK* Madin–Darby bovine kidney, *MIC* minimum inhibitory concentration, *mkr* methicillin–kanamycin resistance, *Na* not applicable, *Nd* not determined, *NOSA* nitric oxide scavenging activity, *Nt* not tested, *P* protection, *PET* petroleum ether, *PE* Paw edema, *PTZ* pentylenetetrazole, *pfr* penicillin-fluoroquinolones resistances, *pr* penicillin resistance, *RMP* resting membrane potential, *R* roots, *Se* seeds, *SGPT* serum glutamate pyruvate transaminase, *SGOT* serum glutamate oxaloacetate transaminase, *S* stems, *Tr* triglycerides, *T* time spent on licking the injected paw, T_3 triiodothyronine, T_4 thyroxine, *t-BHA* 3-tert-butyl-4-hydroxyanisole, *TC* total cholesterol, *TSH* thyroid-stimulating hormone, *TVL* total vessel length, *UI* international units, *VA* vessel area, *VB* vascular branch, *VLDL* very low-density lipoproteins

respectively). Moreover, the 200 mg/kg dose was able to remarkably lower insuline resistance ($P < 0.01$) (Ahangarpour et al. 2014).

D. aucheri was also investigated in a double-blind, placebo-controlled, randomized clinical trial recruiting 170 patients with type II diabetes. They took a gelatine capsule (200 or 500 mg) prepared with the powdered extract obtained from the aerial parts daily. Ater 45 days of treatment, a significant (1.1 to 2.5 folds) increase in PPAR-g expression was observed in patients treated with 500 mg of the extract, compared to the placebo-treated control group ($P < 0.01$). In the same group of patients, the extract also increased plasma superoxide dismutase activity (from 1313.38 to 1444.51 U/g protein) and vascular catalase gene activity (from 79.71 to 90.32 kU/g protein) (Nahvinejad et al. 2016).

Hypolipidemic activity

The study carried out by Ahangarpour et al. (2014) showed that the administration of 100 mg/kg of 30% EtOH extract of *D. aucheri* leaves to nicotinamide/streptozotocin-induced diabetic rats, was able, after 4 weeks, to significantly reduce total cholesterol (TC, 57 mg/dL), triglycerides (Tr, 66.71 mg/dL), very low-density lipoprotein (VLDL, 13.34 mg/dL) and leptin (0.93 ng/dL) levels, compared to diabetic control group characterized by higher values for all the parameters considered (TC, 67.87 mg/dL; Tr, 126.12 mg/dL; VLDL, 25.22 mg/dL; leptin content, 1 ng/dL).

Anti-inflammatory activity

An in vivo study using carrageenan-induced paw edema in mice showed significant dose-dependent anti-inflammatory activity of the aqueous extract of *D. ammoniacum* resin. At the highest dose of 500 mg/kg, less developed edema was recorded. The sample significantly reduced (up to 47%) inflammation compared to the negative control (saline) and its effect was immediately (1 h after the treatment) similar to that of indomethacin (− 33% and − 36%, respectively) used as a positive control (Bakhtiarian et al. 2017). These outcomes were confirmed by Pandpazir and colleagues (2018). Their aqueous extract also showed significant systemic anti-inflammatory activity. All tested doses (100, 200 and 300 mg/kg) were able to inhibit edema in a similar or superior way to that of mefenamic acid (30 mg/kg) used as a positive control, at various time intervals (from 54.1–65.1% vs. 62.4% at 30 min and from 76.7–98.4% vs. 62.8% at 3 h). Topical administration of the *D. ammoniacum* resin extract (100 mg/kg) was less effective. Nevertheless, its action was similar or higher (19.5% and 43.3% inhibition of paw edema, respectively, after 2 and 4 h of application) than that of diclofenac gel 2% (18% and 26.4%) (Pandpazir et al. 2018).

Even some pure compounds such as sesquiterpenes kopetdaghins A (**24**), C (**26**) and E (**28**) from *D. kopetdaghense* were tested for their anti-inflammatory effect showing a remarkable activity. In particular, kopetdaghins (10–100 µg/mL) significantly inhibited, in a concentration-dependent manner, the LPS-induced nitric oxide (NO) release by the activated J774A.1 macrophages. At the highest concentration, all three compounds 100% inhibited the NO production, but kopetdaghin A (**24**) was the most active compound with 57.3%, 77.8%, and 94.2% inhibitions at 10, 20, and 50 µg/mL, respectively (Rabe et al. 2013, 2015).

Antimicrobial activity

The ability of various extracts and EOs of two *Dorema* species—*D. aucheri* and *D. ammoniacum*—against a wide range of microbial strains were analyzed.

The antibacterial activity of 95% MeOH extract from *D. aucheri* aerial parts was assessed against various pathogenic food-altering bacteria, both Gram-negative and Gram-positive. By the disc diffusion and Microtiter broth dilution methods, the extract showed the greatest activity against the Gram-negative bacterium *Salmonella enteritidis* with an inhibition zone (IZ) diameter of 14.3 mm and an inhibition of the growth equal to 99.1%. The IZs of the other treated bacteria ranged from 7.76 to 12.6 mm and their growth was inhibited from 70.6–97.9% (Gheisari et al. 2016).

D. aucheri root $CHCl_3$ extract possessed the highest antibacterial effect against *Shigella flexneri*, with a minimum inhibitory concentration (MIC) of 0.15 µg/mL in microbroth dilution assay. Its potential was higher than that of the reference compound ciprofloxacin (0.156 µg/mL vs. 0.313 µg/mL). However, ciprofloxacin was more effective against *Staphylococcus aureus* (0.156 µg/mL vs. 0.313 µg/mL),

Escherichia coli (0.156 µg/mL vs. 0.625 µg/mL) and *Bacillus subtilis* (0.625 µg/mL vs. 2.50 µg/mL) (Khan et al. 2014). The *n*-hexane extract from *D. aucheri* roots was found even more active. Its MIC values were equal to that of the ciprofloxacin against *Escherichia coli* (0.156 µg/mL), *Staphylococcus aureus* (0.156 µg/mL) and *Shigella flexneri* (0.313 µg/mL), halved against *Bacillus subtilis* (0.313 µg/mL vs. 0.625 µg/mL) (Khan et al. 2014).

Lastly, the antibacterial activities of 80% MeOH extracts obtained from leaves, stems, and flowers of *D. aucheri* against 4 selected bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, and *Salmonella enterica*) were studied. None of the extracts was able to inhibit the growth of *Escherichia coli*, while the leaf and flower samples showed the maximum activity against *Staphylococcus aureus* with MIC of 10 mg/mL. In general, the stems were the least effective organs against all bacteria (MICs from 20 to 40 mg/mL) (Mianabadi et al. 2015).

As for *D. ammoniacum*, the agar dilution-streak was used to evaluate the antimicrobial activity of the DCM-MeOH (1:1) resin extract in two studies. In the work of Kumar et al. (2006), the extract (500 and 1000 µg/ml) completely inhibited the growth of almost all tested bacteria (*Bacillus cereus* var. *mycoides*, *Bacillus pumilus*, *Bacillus subtilis*, *Bordetella bronchiseptica*, *Micrococcus luteus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Streptococcus faecalis*) and fungi (*Candida albicans*, *Aspergillus niger*, *Saccharomyces cerevisiae*), similarly to the positive controls ciprofloxacin (3 µg/mL) and amphotericin-B (3 µg/mL). Previously, Rajani and colleagues (2002) reported that the same extract had no inhibitory action against the same microorganisms at concentrations of 10 and 20 µg/mL. The complete inhibition of their growth, comparable to that due to ciprofloxacin (2 µg / mL), was recorded at higher concentrations (40, 60, 100 and 200 µg / mL). Only *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Candida albicans* were not sensitive to the effect of *D. ammoniacum* resin at any used concentration.

In a screening study on the antimicrobial activity of 36 plant species against a broad spectrum of pathogenic and multidrug-resistant microrganisms, including 35 bacteria and 1 fungus, the MeOH extract of *D. ammoniacum* seeds was one of the most active. Its bactericidial activity was characterized by the lowest MIC and MBC values (78 and 312 µg/mL, respectively) against 2 *Staphylococcus aureus* strains, *Staphylococcus epidermidis* and *Staphylococcus lugdunensis*. Although the fungicidal activity had a MIC (0.6 µg / mL) lower than the control (amphotericin B, $\leq$ 1 µg / mL) in the preliminary phase of the study, it was not significant in the more refined subsequent measurement (Abedini et al. 2014).

Interestingly, the aqueous extract of *D. ammoniacum* aerial parts used to synthesize silver nanoparticles (SNPs) increased their antibacterial effectiveness compared to $AgNO_3$ solution used as a positive control. SNPs showed a stronger activity against all tested bacteria, namely *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhimurium* (IZs, 9.4, 9.2, 10.7, and 9.0 mm vs. 8.5, 9.0, 9.1 and 8.0 mm, respectively). The highest effect against *Escherichia coli* was confirmed by the MIC (0.12 µg/mL) and MBC (0.23 µg/mL) values (Zandpour et a. 2018).

In addition, also the EO extracted from fruits of *D. ammoniacum* was subjected to antimicrobial activity assessment using seven bacteria (*Bacillus subtilis*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) and three fungi (*Candida albicans*, *Saccharomyces cerevisiae* and *Aspergillus niger*). The results revealed that the EO had the highest IZs (23 and 22 mm) and MIC values (3.75 mg/mL) against *Bacillus subtilis* and *Staphylococcus epidermidis*, respectively. Nevertheless, only in the case of *Bacillus subtilis*, EO showed greater inhibition than that of the antibiotic tetracycline (30 µg/disc, IZ = 21 mm) (Yousefzadi et al. 2009; 2011).

Antiplasmodial activity

Natural sources of potential products effective in the fight against malaria have been extensively studied, including *Dorema* species. EtOAc extract of *D. hyrcanum* roots (10 mg/kg) demonstrated a marked inhibition (by 73%) of *Plasmodium berghei* growth assessed by Peter′s 4-day suppressive test on mice, although lower than the effect of chloroquine (20 mg/kg) showing 100% inhibition. In addition, among the secondary metabolites isolated from the extract, naghibione (**29**) (10 mg/kg) inhibited the parasite growth by 68.1%, followed by 2,3-dihydro-7-

methoxy-2 S *,3R*-dimethyl-2-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c]coumarin (**8**) (29.3%), 2,3-dihydro-7-ethoxy-2R*,3R*dimethyl2-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c]coumarin (**9**) (23.3%) and acetophenon (**22**) (10.1%) (Naghibi et al. 2015).

In a screening phase, via using parasite lactate dehydrogenase method, in vitro antiplasmodial activity of the MeOH extract of *D. hyrcanum* roots against both chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *Plasmodium falciparum* reported IC_{50} values equal to 28.64 µg/mL and 9.79 µg/mL, respectively (Naghibi et al. 2015).

Antioxidant activity

Different soluble extracts obtained from various parts of three *Dorema* species including *D. aitchisonii*, *D. aucheri*, and *D. glabrum* were investigated for their antiradical activity. For example, EtOH extract of *D. aitchisonii* aerial parts was characterized by an IC_{50} value equal to 488.1 µg/mL indicating a weak scavenger activity against the free radical DPPH compared to reference compounds ascorbic acid, quercetin, and BHA (butylated hydroxy anisole) (IC_{50} = 5.05, 5.28, and 53.96 µg/mL, respectively). The low effect was confirmed by ICA (nitric oxide scavenging activity) method, where the IC_{50} value (778.2 µg/mL) was 40 times higher than that of EDTA (18 µg/mL) used as a positive control. NOSA (nitric oxide scavenging activity) and HPSA (hydrogen peroxide scavenging activity) results also showed a low activity of the extract (IC_{50} = 1300 and 210.6 µg/mL, respectively) compared to quercetin (IC_{50} = 20 and 52 µg/mL, respectively) (Nabavi et al. 2012).

In another experiment, the DPPH assay was used to evaluate the radical scavenging activity of crude petroleum ether (PET), $CHCl_3$, EtOAc, and MeOH extracts obtained from *D. glabrum* aerial parts, together with the isolated compounds. Among the extracts, MeOH fraction was the most effective with an IC_{50} of 48.3 µg/mL, while the lowest IC_{50} (2.23 µg/mL), almost 9 times less than that of the BHT control (IC_{50} = 19.5 µg/mL), was found for chlorogenic acid (**35**) (Delnavazi et al. 2015).

In a comparitive study by Khan et al. (2014) on the roots of *D. aucheri*, the results of DPPH assay showed that *n*-hexane extract (IC_{50} = 104.3 µg/mL) was more active than $CHCl_3$ extract (IC_{50} = 132.4 µg/mL). However, this effect was significantly less than those of the *n*-propyl gallate (IC_{50} = 40.8 µg/mL) and *t*-BHA (IC_{50} = 59.8 µg/mL) positive controls.

In the FRAP assay, the MeOH extract of *D. aucheri* stems and flowers was able to reduce the ferric ion (Fe^{3+}) more effectively than the extract obtained from the leaves (4.33 Fe^{2+}/g and 4.22 mmol Fe^{2+}/g vs. 1.7 mmol Fe^{2+}/g). Stems and flowers also demonstrated the highest activity in the inhibition of lipid peroxidation obtained by applying β-carotene bleaching method (Mianabadi et al. 2014).

Antiproliferative and cytotoxic activity

In an in vivo study on rats, the effect of 50% EtOH extract of *D. aucheri* plants on breast tumour induced by 7,12-dimethylbenz[a]anthracene (DMBA) was evaluated. The obtained results indicated that, after 12 weeks, the tumour average size in the groups that took orally 200 mg/kg or 400 mg kg of extract every day was 152.92 mm and 444.14 mm, respectively. Otherwise, in the control groups, the tumour average size was 746.2 mm (Gourabi et al. 2015).

Eftekhari et al. (2019) used the MTT test to investigate the cytotoxic activity of different extracts (PET, $CHCl_3$, EtOAc and MeOH) obtained from the *D. aucheri* aerial parts against MDA-MB-231 (breast cancer), A549 (lung carcinoma), HT-29 (colon carcinoma), HeLa (cervical cancer) and normal fibroblast cell lines. Of all the samples, PET and $CHCl_3$ extracts were the most potent cytotoxic agents (IC_{50} = 17.00 and 69.7 µg/mL, respectively) against normal fibroblast and MDA-MB-231 cell lines.

The MTT assay also showed that chlorogenic acid (**35**) isolated from *D. glabrum* roots significantly increased apoptosis and hindering cell cycle progression accompanied by upregulation of Bax and caspase 3 gene expression in adenocarcinoma gastric cell line (Jafari et al. 2018). In addition, both the root EtOH extract and the pure compound naghibione (**29**) were analyzed to assess their cytotoxic potential against Madin–Darby bovine kidney cell line. The crude extract showed better activity (IC_{50} = 69.67 µg/mL) than the isolated sesquiterpene (IC_{50} > 100 µg/mL). However, both samples were much less active than the positive control tamoxifen (IC_{50} = 4.76 µg/mL) (Naghibi et al. 2015).

Antithyroid activity

The 50% EtOH extract from *D. aucheri* aerial parts (100, 200 and 400 mg/kg) was evaluated for its activity on thyroid hormones (TSH, T_3 and T_4) in Wistar rats. After 3 weeks of administration, only the lowest dose (100 mg/kg) significantly increased TSH levels (11.63 ng/dL) compared to the control group (0.84 ng/dL). Differently, the concentrations of T_3 and T_4 hormones were similar in all studied groups regardless of the extract dosage (Azarneushan et al. 2010).

Hepatotoxic activity

Two in vivo studies investigated the hepatotoxic effect of *D. aucheri* leaves. Mostafavi et al. (2013) reported that the 95% EtOH extract increased the levels of liver enzymes serum glutamate pyruvate transaminase (SGPT) from 179.89 to 263.5 IU (international unit)/L, serum glutamate oxaloacetate transaminase (SGOT) from 93.60 to 131.51 IU/L, and alkaline phosphatase (ALP) from 189.09 to 295.44 IU/L, by increasing the injection dosage of the extract from 0.4 to 3.2 mL/kg, respectively. Otherwise, SGPT, SGOT, and ALP contents were lower in case of the non-injected control group (86.43, 37.81, and 181.43 IU/L, respectively). The study also analyzed liver homogenates and it was found that the injection of the plant extract altered liver function causing necrosis, inflammation of the liver tissue, cell proliferation, cholestasis and significant increase in bilirubin levels (up to 1.86 mg/dL) compared to the control groups (Mostafavi et al. 2013).

In addition, the leaves of *D. aucheri* were extracted with 30% EtOH and injected into the streptozotocin-induced diabetic rats. The most effective concentration of the extract on the level of hepatic enzymes SGPT (37.71 ng/dL), SGOT (86.62 ng/dL), and ALP (112 ng/dL) was 200 mg/kg. These values were similar to or lower than those of the control group (56.25, 87, and 117.12 ng/dL, respectively) and the diabetic group (67, 126.62, and 139.25 ng/dL) (Ahangarpour et al. 2014).

Neuronal activity

The intracellular recording assay was used to explore the effect of *D. ammoniacum* resin on the epileptiform activity of F1 neurons in *Helix aspersa* (Iranian garden snail) induced by pentylenetetrazole (PTZ). The results demonstrated that increasing dosage of the extract (0.01–0.3%), applied as an epileptic drug, enhanced the hyperexcitability induction and epileptiform activity by depolarizing the membrane potential from − 32.91 to − 39.16 mV, increasing the firing frequency from 3.39 to 3.47 Hz and decreasing the after hyperpolarization amplitude (AHP) from − 1.263 to − 1.122 mV. All this suggests that the sample potentiated the PTZ-induced hyperexcitation by electrophysiologically suppressing the Ca^{2+} and/or voltage-dependent K^+ channels (Ghasemi et al. 2018).

Vascular toxicity

The vascular toxicity of *D. ammoniacum* resin was recently demonstrated. Fertilized chicken eggs were inoculated with 20% EtOH extract (50 or 100 mg/kg egg-weight) and the vascular network parameters were altered compared to those of the control group. In particular, after treatment with 100 mg/kg of extract, the vessel area significantly decreased from 63.3–39.2% as well as the total vessel length (from 8721.32 pixel to 722.84 pixel) and the vascular branch (from 132 to 48), while the lacunarity increased from 0.33 to 0.91 (Tavakkoli et al. 2020).

Conclusions

The species of the genus *Dorema*, particularly *D. ammoniacum* (oleo gum resin) and *D. aucheri* (aerial parts) are traditionally used as medicine and food in Middle East, especially in Iran. In the last years, the phytochemistry of the *Dorema* species were considered as a promising research field. Regarding this issue, among the 12 accepted species, only 6 and 3 species, respectively, were investigated for their non-volatile and volatile phytoconstituents.

According to the results obtained from the phytochemical analyses, phenolic acids, flavonoids, acetophenones, coumarins and sesquiterpenes are the main secondary metabolite classes of the *Dorema* genus. In particular, coumarin and acetophenone derivatives may be presumed as the predominant compounds of the genus. Most of the reported coumarins and flavonoids were isolated from the roots and aerial parts. The roots also provided all the

acetophenones and most of the sesquiterpenes. The phenolic acids were present in almost all plant parts.

Among the identified phytochemicals, kopetdaghin A (**24**), kopetdaghin B (**25**), and kopetdaghin C (**26**) from *D. kopetdaghense*, and naghibione (**29**) from *D. hyrcanum*, along with (2′S,5′S)-2′-ethenyl-5′-(3-hydroxy-6-methyl-4-oxohept-5-en-2-yl)-7-methoxy-2′-methyl-4H-spiro[chromene-3,1′-cyclopentane]-2,4-dione (**1**) and doremone A (**2**) from oleo gum resin of *D. ammoniacum* were isolated as new secondary metabolites.

The leaves were the richest organs in EO. It was mainly composed of sesquiterpenes as aromatic components, although the most abundant volatile oil constituents included also monoterpenes.

So far, the bioactivity of only 6 *Dorema* species, namely *D. aitchisonii*, *D. ammoniacum*, *D. aucheri*, *D. glabrum*, *D. hyrcanum*, and *D. kopetdaghense*, were studied. Among them, *D. ammoniacum* and *D. aucheri*, were the most tested species. Some of the most significant results, higher than those of the used positive controls, concern (i) the anti-inflammatory activity of the topical application of the *D. ammoniacum* resin extract, (ii) the antibacterial effect of the $CHCl_3$ extract of *D. aucheri* roots, (iii) increasing TSH level by 50% EtOH extract of *D. aucheri* aerial parts, (iv) the hypolipidemic activity of EtOH extract from *D. aucheri* leaves.

As for the other uninvestigated 6 species, they may be assumed as promising plant material for further experiments, both in vitro and in vivo, to discover new sources of compounds potentially interesting as natural drug candidates. Moreover, since some of these species are traditionally consumed as food, the evaluation of their safety and toxicity is indispensable.

Compilance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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