Published online: 2019-06-19

A Review of the Phytochemistry, Traditional Uses, and Biological Activities of the Genus *Ballota* and *Otostegia*[1]

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Key words
Ballota, *Otostegia*, secondary metabolites, antioxidant, antibacterial, antifungal

received January 24, 2019
revised June 5, 2019
accepted June 7, 2019

Bibliography
DOI https://doi.org/10.1055/a-0953-6165
Published online June 19, 2019 | Planta Med 2019; 85: 869–910 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0032-0943

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ABSTRACT

The 2 genera *Ballota* and *Otostegia*, belonging to the Lamiaceae family, are closely related taxonomically and found mainly in the Mediterranean area, Middle East, and North Africa. Since ancient times, they have been largely employed in traditional medicine for their biological properties such as antimicrobial, anti-inflammatory, antispasmodic, insecticidal, anti-malaria, etc. Phytochemical investigations of *Ballota* and *Otostegia* species have revealed that diterpenoids are the main constituents of the genera. A large number of flavonoids and other metabolites were also identified. This review, covering literature from 1911 up to 2018, includes traditional uses, chemical profiles (both of volatile and nonvolatile metabolites), and biological properties of all the taxa of these 2 genera studied to date.

Introduction

The genus *Ballota*, belonging to Lamiaceae family (Stachyoideae/Lamioideae subfamily) [1, 2], is, apart from the South African endemic species *Ballota africana* (L.) Benth., naturally distributed in the Mediterranean, the Middle East and in North Africa. Some species (e.g., *Ballota nigra* L. s. l.) are also present over large areas of western, central, and northern Europe, and 4 species, whose status will be discussed later, in Somalia.

Ballota species are perennial herbs or small shrubs with branched and/or simple hairs, toothed and petiolate leaves, the inflorescence thyrsoid or racemoid sometimes has long and spinose bracteoles (sect. Acanthoprasium), and the calyx is mostly campanulate, purple to white.

A former classification of the genus identified the occurrence of 31 species (1 = *Ballota integrifolia* Benth. – 2 = *Ballota wettsteinii* Rech. pat. – 3 = *Ballota frutescens* (L.) Woods – 4 = *Ballota fruticosa* Baker – 5 = *Ballota somala* Patzak – 6. *Ballota andreuzziana* Pamp. – 7 = *Ballota acetabulosa* (L.) Benth. – 8 = *Ballota undulata* (Sieb, ex Fres.) Benth. – 9 = *Ballota pseudodictamnus* (L.) Benth. – 10 = *Ballota damascena* Boiss. – 11 = *Ballota hildebrandtii* Vatke et Kurtz – 12 = *Ballota hirsuta* Benth. – 13 = *Ballota bullata* Pomel – 14 = *B. africana* (L.) Benth. – 15 = *Ballota aucheri* Boiss. – 16 = *Ballota macrodonta* Boiss. et Bal. – 17 = *Ballota larendana* Boiss. et Heldr. – 18 = *Ballota rotundifolia* C. Koch – 19 = *Ballota rupestris* (Biv.) Vis. – 20 = *Ballota macedonica* Vand. – 21 = *Ballota kaiseri* V. Täckh. – 22 = *Ballota antilibanotica* Post – 23 = *Ballota cristata* Davis – 24 = *Ballota semanica* Rech. f. – 25 = *Ballota labillardieri* Briq. – 26 = *Ballota saxatilis* Sieb. ex J. et C. Presl – 27 = *Ballota stachydiformis* Höchst. – 28 = *Ballota philistea* Bomm. – 29 = *Ballota platyloma*

[1] Dedicated to Professor Dr. Cosimo Pizza in recognition of his important contributions to natural product research on the occasion of his 70th birthday in 2019.

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ABBREVIATIONS

ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
Ac	acetone
AD	agar diffusion
ALP	alkaline phosphatase
AP	aerial parts
BuOH	butanol
CAT	catalase
CQ	chloroquine
CUPRAC	cupric ion reducing antioxidant capacity
DPPH	2,2-diphenyl-1-picrylhydrazyl
EO	essential oil
EtOAc	ethyl acetate
EtOH	ethanol
F	flowers
FRAP	ferric reducing antioxidant power
GSH	gluthatione
L	leaves
LPO	linoleic acid peroxidation
MBC	minimum bactericidal concentration
MeOH	methanol
MIC	minimum inhibiting concentration
MPO	myeloperoxidase
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
n-Hex	*n*-hexane
NO	nitric oxide
NOE	nuclear Overhauser effect
ORAC	oxygen radical absorbance capacity
PE	petroleum ether
R	root
S	stems
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamine-pyruvate transaminase
SOD	superoxide dismutase
STZ	streptozotocin
TB	total bilirubin
TBARS	thiobarbituric acid reactive substances
TEAC	Trolox equivalent absorbance capacity
TG	triglycerides
VLDL	very low density lypoproteins
W	water
WP	whole plant
X/XO	hypoxanthine/xanthine redox couple

Rech. f. – 30 = *B. nigra* L. – 31 = *Ballota royleoides* Benth.) which were divided into 10 sections [3–5].

In subsequent years, several modifications and additions were made to the former classification.

The 4 Somalian species, *B. fruticosa, B. somala, B. hildebrandtii*, and *B. stachydiformis* were moved to other genera and now their accepted names are *Otostegia modesta* S. Moore, *Isoleucas somala* (Patzak) Scheen (syn. *Otostegia somala* (Patzak) Sebald), *Otostegia hildebrandtii* (Vatke & Kurtz) Sebald, and *Leucas stachydiformis* (Benth.) Hochst. ex Briq., respectively [6]; *B. integrifolia* and *B. wettsteinii* are both considered synonyms of *Acanthoprasium integrifolium* (Benth.) Ryding (accepted name) [7]; *B. frutescens, B. labillardieri, B. semanica*, and *B. rupestris* are synonyms of *Acanthoprasium frutescens* (L.) Spenn. [7], *B. saxatilis, B. saxatilis* subsp. *brachyodonta* (Boiss.) P.H. Davis & Doroszenko, and *Ballota hispanica* (L.) Benth., respectively [6].

The Plant List [6], which has been used to validate the scientific names of the species, includes more than 160 scientific plant names of species rank for the genus *Ballota*. Of these, only 30 are accepted species names.

The genus *Otostegia* (Lamiaceae family, Stachyoideae/Lamioideae subfamily), closely related to genus *Ballota* morphologically, with about 15 species, occurs in rather dry, often montane areas and semideserts [8]. There are 2 clearly disjoint centers of diversity for *Otostegia*: Central Asia to Afghanistan and northeastern Africa [9], although the genus is distributed from Cameroon to Saudi Arabia, Yemen, Egypt, Iran, and Central Asia to India [8].

In 2007, Scheen & Albert [10] proposed to restrict the *Otostegia* genus, including only the following 11 species in it: *Otostegia ellenbeckii* Gürke, *Otostegia ericoidea* Ryding, *Otostegia erlangeri* Gürke, *Otostegia fedtschenkoana* Kudr., *Otostegia fruticosa* (Forssk.) Schweinf. ex Penzig, *O. hildebrandtii, Otostegia migirtiana* Sebald, *O. modesta, Otostegia olgae* (Regel) Korsh., *Otostegia sogdiana* Kudr., and *Otostegia tomentosa* A. Rich. The former members of *Otostegia, O. somala* and *Otostegia aucheri,* were transferred to *Isoleucas* and *Moluccella*, respectively. A new genus was erected for the 4 yellow-flowered species of *Otostegia* (*Otostegia integrifolia* Benth., *Otostegia limbata* [Benth.] Boiss, *Otostegia michauxii* Briq., *Otostegia persica* (Burm. f.) Boiss), for which the name *Rydingia* A.-C. Scheen & V.A. Albert was proposed. Consequently, the 4 names actually accepted for these species are *Rydingia integrifolia* (Benth.) Scheen & V.A. Albert, *Rydingia limbata* (Benth.) Scheen & V.A. Albert, *Rydingia michauxii* (Briq.) Scheen & V.A. Albert, *Rydingia persica* (Burm. f.) Scheen & V.A. Albert [6].

The Plant List [6] is generally in agreement with this classification of genus *Otostegia*. It reports 46 name records of species rank for the genus *Otostegia*, of which only 10 species and 3 subspecies are accepted. In addition to the above-mentioned species [10], the Plant List added *Otostegia nikitinae* Scharasch. and *Otostegia schennikovii* Scharasch., while moving *Otostegia bucharica* B. Fedtsch., *O. fedtschenkoana, O. olgae*, and *O. sogdiana* to genus *Moluccella* [7].

In this review, a complete survey of the traditional uses, chemical constituents (both volatile and nonvolatile), and biological properties of species from the genera *Ballota* and *Otostegia* is provided.

The available information on these genera was collected from scientific databases and cover from 1911 up to 2018. The following electronic databases were used: PubMed, SciFinder, Science Direct, Scopus, Web of Science, and Google Scholar.

The search terms used for this review included *Ballota, Otostegia*, all the botanical names of the species, both accepted names or synonyms, phytochemical composition, EOs, traditional uses, activity, pharmacology, and toxicity. No limitations were set for languages. ▸ **Table 1** reports the taxa of *Ballota* and *Otostegia* investigated so far, their synonyms, and the accepted botanical names.

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▶ **Table 1** *Ballota* s. l. and *Otostegia* s. l. taxa studied so far and their synonymous (accepted botanical name in bold).

Taxa	Synonyms
Ballota acetabulosa **(L.) Benth.**	
Ballota africana **(L.) Benth.**	
Ballota andreuzziana **Pamp.**	
Ballota antalyensis Tezcan & H. Duman	
Ballota arabica Hochst. & Steud.	***Leucas urticifolia*** **(Vahl) Sm.**
Ballota aucheri **Boiss.**	*Otostegia aucheri* Boiss.
Ballota cinerea D. Don	***Roylea cinerea*** **(D. Don) Baill.**; *Roylea calycina* (Roxb.) Briq.; *R. elegans* Wall. ex Benth.
Ballota cristata **P. H.Davis**	
Ballota deserti **(Noë) Jury, Rejdali & A. J. K.Griffiths**	*Marrubium deserti* (Noë) Coss.
Ballota glandulosissima **Hub.-Mor. & Patzak**	
Ballota hirsuta **Benth.**	
Ballota hispanica **(L.) Benth.**	*Ballota rupestris* (Biv.) Vis.
Ballota inaequidens **Hub.-Mor. & Patzak**	
Ballota lanata L.	***Panzerina lanata*** **(L.) Soják**; *Panzeria alaschanica* Kuprian.; *P. lanata* (L.) Bunge
Ballota larendana **Boiss. & Heldr.**	
Ballota latibracteolata **P. H. Davis & Doroszenko**	
Ballota macrodonta **Boiss. & Balansa**	
Ballota nigra **L.**	
B. nigra L. subsp. *anatolica* P. H.Davis	
Ballota nigra **subsp.** ***foetida*** **(Vis.) Hayek**	
Ballota nigra f. *uncinata* Beg,	***Ballota nigra*** **subsp.** ***ruderalis*** **(Sw.) Briq.**
Ballota philistaea **Bornm.**	
Ballota pilosa Lour.	***Leucas chinensis*** **(Retz.) Sm.**; *L. mollissima* subsp. *chinensis* (Benth.) Murata
Ballota pseudodictamnus **(L.) Benth.**	
Ballota pseudodictamnus subsp. *lycia* Hub.-Mor	
Ballota rotundifolia **K. Koch**	
Ballota rupestris (Biv.) Vis.	***Ballota hispanica*** **(L.) Benth.**
Ballota saxatilis **Sieber ex C.Presl**	
Ballota saxatilis **subsp.** ***brachyodonta*** **(Boiss.) P. H.Davis & Doroszenko**	
Ballota schimperi Benth.	***Otostegia fruticosa*** **subsp.** ***schimperi*** **(Benth.) Sebald**
Ballota sechmenii **Gemici & Leblebici**	
Ballota undulata **(Sieber ex Fresen.) Benth.**	
Otostegia fruticosa **(Forssk.) Schweinf. ex Penzig**	
Otostegia fruticosa **subsp.** ***schimperi*** **(Benth.) Sebald**	***Otostegia fruticosa*** **subsp.** ***schimperi*** **(Benth.) Sebald**
Otostegia integrifolia Benth.	***Rydingia integrifolia*** **(Benth.) Scheen & V. A.Albert**
Otostegia limbata (Benth.) Boiss.	***Rydingia limbata*** **(Benth.) Scheen & V. A.Albert**; *Ballota limbata* Benth.
Otostegia persica (Burm.f.) Boiss.	***Rydingia persica*** **(Burm.f.) Scheen & V. A.Albert**; *Ballota persica* (Brum.f.) Benth
Otostegia tomentosa **A.Rich.**	

Traditional Uses

Several plant species belonging to *Ballota* and *Otostegia* genera have been used in traditional medicine of many countries. A summary of their traditional use is presented in ▶ **Table 2**.

In Europe, the most utilized is, by far, *B. nigra*, a perennial herb native to the Mediterranean region and to central Asia, which can be found throughout Europe. It is also naturalized in Argentina, New Zealand, and the eastern United States. Leaves of *B. nigra* were used as an antidote for rabid dog bites. It was used in the Balkanic area as a sedative/tranquilizer in cases of hysteria and hypochondria [31, 32, 37, 38]. It is also used in Italy externally, for wound-healing properties [33, 36]. Internally, in the Balkans, it is used as a sedative, a spasmolytic for stomach cramps and aches, for whooping cough, and to increase bile flow. It is also used to treat nervousness, upset stomach, nausea, and vomiting [30,

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38]. In Moldova, in the form of enemas and suppositories, it is used against worm infestation [31]. In northern Spain, it is used as insecticide and repellent against fleas [39]. In several parts of Turkey, its subspecies *B. nigra* L. subsp. *anatolica*, where it is known by different vernacular names, has been reported for the treatment of cold and flu [43], flatulence, and upset stomach [41] and as antiseptic for wounds, burns, and inflamed skin [40, 42]. *B. acetabulosa*, known as the Greek horehound, is a compact, evergreen subshrub, growing to 0.5 m, native to southeast Greece, Crete, and western Turkey. In Turkey, the infusion of leaves is used for treatment of stomach ailments, where the leave poultice relieves abdominal pain and hemorrhoids [11, 12].

In the southern part of Africa, the only species present is *B. africana*, known as Cape horehound or "kattekruie." It is most common in the more arid, winter rainfall areas of the Cape. Its natural distribution stretches from the southern part of Namibia down to the West Coast and Cape Peninsula. Along this wide distribution, *B. africana* is usually found along streams and in the shelter of rocks and bushes. Externally, a leaf compress is applied on sick children's feet, on painful legs, inflamed joints, backache, head for headache, on cheek for toothache, on breasts for mastitis, wash for chilblained hands and feet, wounds, ointment on sores, and as poultice on boils. Orally, leaf infusion is used for stomach ache, influenza, fever, asthma, lung, and urinary infections, to treat convulsions in infants, to wean infants, and as cough syrup [13–15].

Ballota deserti (syn. *Marrubium deserti*) is a common endemic species in the northern and central Sahara. In Tunisia, it is employed in traditional medicine in the form of a decoction as a remedy for asthma, diabetes, and as a diuretic [25]. The internal usage of this species has been documented in the central Sahara using the infusion of its leaves for respiratory diseases, fever, colic, colds, cough, digestive troubles, helminthiasis, and nausea [23, 24]. Another plant utilized in North Africa (High Atlas, Morocco, and West Algeria) is *B. hirsuta*, native to the western Mediterranean region, mostly abundant in Spain, Portugal, and North Africa. It is very popular with traditional healers (known as "uarimsa," "tougan'if-zi," or "tifziguiyin") as a cure for many diseases. The poultice of leaves and roots is used very often to treat subcutaneous lesions (contusion), rheumatic pains, and heal various wounds. The decoction of flowers is used externally as an antiseptic or orally against dental caries, whereas the flower infusion is utilized internally to treat gastrointestinal, gynecological and pediatric diseases [26, 27].

In East Africa (Eritrea, Ethiopia), there are many reports of some *Otostegia* species concerning their usage in traditional medicine. The most numerous data are available for *O. integrifolia* (syn. *R. integrifolia*). *O. integrifolia*, commonly known as Abyssinian rose, is endemic to Ethiopia, where it is known as "tinjute" (ጥንጁት), growing in the dry evergreen woodlands regions at altitudes of 1300–2800 m above sea level. It also grows in Eritrea and Yemen. In northern Ethiopia, it is commonly used to smoke utensils for sterilization. It is also a ritual custom for a mother to cleanse herself with the smoke on the tenth day after giving birth to a child before leaving her confinement to resume normal daily activities [56]. It has been largely employed as an insect repellent against fleas and mosquitos and as antimalarial [47, 50, 52, 53]. Inhalation of the smoke of burnt stems and leaves is used against evil eye [48, 51] and its juice, diluted with water, is drunk for treatment of stomach ache, vomiting, nausea, diarrhea, and dysentery [46, 51]. In the same geographical area, the juice of *O. tomentosa* and *O. fruticosa* has been similarly used against diarrhea [46], and the latter also against ascariasis [46] and tonsillitis [48].

O. fruticosa also grows in the Arabic peninsula where the infusion of flowering branches is used as a remedy for sun-stroke [49] or as an anti-paralytic and for eye diseases [44, 45].

In Pakistan, India and Iran, species belonging to *Ballota* and *Otostegia* genera have been largely employed in traditional medicine.

B. arabica (syn. *Leucas urticifolia* (Vahl) Sm.) is an annual herb distributed in the Punjab, Baluchistan, Sindh, and Rajputana desert of Pakistan. In Baluchistan, where it is known as "kubo" or "goma," the plant is used as a cure for fever. Furthermore, the decoction of the leaves and apical shoots is used as an abortifacient up to 3 mo of pregnancy. Infusions of the flowers are used to treat skin diseases. The plant is also used for the treatment of diarrhea, dysentery, uterine hemorrhages, dropsy, gravel, cystitis, calculus, bronchial catarrh, skin diseases, fever, and various types of mental disorders [16]. The decoction of leaves, roots and flowers of *B. aucheri* is topically employed in both Pakistan and Iran as hair tonic, for strengthening gums, dental cleaning and brightness, and prevention of hair loss [17, 18]. While in Baluchistan, Iran, the decoction of leaves and flowers of *O. persica* ("golder") is drunk for treatment of diabetes, rheumatism, cardiac distress, palpitation, hypertension, cold, hyper lipidemia, gastric discomfort, headache, and as parasite repellent, sedative, laxative, carminative, and antipyretic [17]. In Pakistan, the largest number of ethno-pharmacological reports involve *O. limbata*. In fact, it is extensively utilized by traditional practitioners against several ailments since it possesses antispasmodic, antiulcer, antidepressant, sedative, and anxiolytic properties [68]. *O. limbata* is consumed for the treatment of children's gum problems and for remedial purposes in cases of ophthalmia [57–59, 61, 63]. Local, fresh leaves of *O. limbata* are crushed and then grounded and mixed with water to make the extract which is also used to cure eye infections. Due to its antiseptic and antibacterial properties [65], powder of dried leaves is mixed with butter and layered on wounds and boils in both humans and animals [59, 65, 69]. Dried plant powder is also utilized against jaundice [61, 63].

Ballota cinerea D. Don is vernacularly known as Karui, Titpatti, or Patkarru. WP parts are widely used as folk medicine in India and Nepal. Shoots are crushed and eaten with salt to strengthen the liver by local villagers. Young shoots are used as insect repellent for cattle during rainy season. Leaves and shoot extraction are used in scabs and other skin infections. AP are widely used to treat malaria and various liver disorders like jaundice, liver debility, and fever [20, 21].

The traditional uses of *Ballota* and *Otostegia* species are wide and sometimes may be directly correlated to the content of some active class of compounds. Along with diterpenes that characterize these species, flavonoids and phenolic compounds, the latter ones often occurring as esters moieties, are the main constituents of the plant extracts and their antibacterial and anti-inflammatory activities are well documented in literature. They could be responsible for most of the claimed remedies. In the following sections the metabolic profiles and the biological activities of these plants have been analyzed.

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▶ **Table 2** Ethnopharmacological uses of *Ballota* and *Otostegia* taxa.

Species	Vernacular names	Area	Use	Ref
B. acetabulosa	boz ot	Aydin, Turkey	stomach ailments, abdominal pain	[11]
		Balikesir, Turkey	hemorrhoid treatment	[12]
B. africana	kattekruid, oulap	Namaqualand, South Africa	stomach ache, headache, backache, wounds, pediatric, coughs and bronchitis, chest ailments, toothache, burning feet, earache, convulsions, weaning, chil-blained hands and feet, mastitis	[13]
	kattekruid	South Africa	fever, cough, asthma, lung infections, influenza, insomnia, stress	[14, 15]
B. arabica	kubo, goma	Baluchistan, Pakistan	abortifacient, astringent, stimulant, hemostatic, anthelmintic, diuretic	[16]
B. aucheri	golder	Baluchistan, Iran	hair tonic, strengthening gums, dental cleaning and brightness, prevention of hair loss	[17]
	chashing	Gilgit Baltistan, Pakistan	hair tonic, dental cleaning	[18]
B. cinerea	kori	Himachal Pradesh, India	stomachache, analgesic	[19]
	karui	Uttarakhand, India	fever, jaundice, skin disease, malaria and most prominently in diabetes	[20, 21]
	karui, titpati, patkarru	Nepal, Kashmir	fever, jaundice, scabs, skin disease, malaria, insect repellent	[22]
B. deserti	telheret, meriout	Central Sahara	respiratory diseases, fever, colics, colds, cough, digestive troubles, helminthiasis, nausea	[23, 24]
		Tunisia	asthma, diabetes, diuretic	[25]
B. hirsuta	uarimsa, touga-n'if-zi, tifziguiyin	High Atlas, Morocco	general health, gastrointestinal, gynecological, pediatric	[26]
		West Algeria	contusion, injuries and rheumatic pain	[27]
B. lanata		Mongolia	treatment of pelvic inflammation and chronic pelvic inflammation, edema, irregular menstruation, dysmenorrheal, amenorrhea, nephritis	[28]
	gang ga' chung	Tibet	stomach, intestinal, and gynecological diseases	[29]
B. nigra		Sharr Mt., Macedonia	digestive	[30]
		Moldova	sedative, antispasmodic stimulant, vermifuge	[31]
	crna kopriva	Northeast Bosnia-Herzegovina	nervous system disorders, sedation	[32]
	erbo moro	Lucca, Italy	against wounds and sprains	[33]
		Mediterranean Area	skin disorders, sore throat in horses	[34]
	bar qene	Albanians, North Basilicata, Italy	diuretic, hemostatic	[35, 36]
	crna kopriva	Bosnia-Herzegovina	hysteria	[37]
		Jadovnik Mt., Serbia	remedy for upset stomach, nausea, and vomiting; symptomatic, treatment of nervous disorders, sleep disorders, coughs, inflammation, gout	[38]
	malrubio negro	North Spain	insecticides and repellents against fleas	[39]
B. nigra L. subsp. *anatolica*	leylimkara	Mersin, Turkey	antiseptic for wounds, to treat inflamed sore in armpit or foot	[40]
	elkurtaran	Taurus Mt., Turkey	to treat flatulence and stomach upset	[41]
	pemberenkli, oğul otu, arı oto	Gönen, Turkey	burns, wounds, headache	[42]
	grip otu	Kırklareli, Turkey	cold, flu	[43]
O. fruticosa		Yemen	anti-paralytic and for eye diseases	[44, 45]
		North Ethiopia	diarrhea	[46]
	sasa	Tigray, Ethiopia	repellent of mosquitos	[47]
	geram tungut	Central Ethiopia	tonsillitis	[48]
	shakab, sharm	Saudi Arabia	remedy for sun-stroke	[49]

cont.

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▶ **Table 2** *Continued*

Species	Vernacular names	Area	Use	Ref
O. integrifolia	cheindog	Eritrea	against fleas and mosquitos	[50]
	tinjute	Ethiopia	stomach-ache, evil eye, fever	[51]
	tinjute	Ethiopia	repellent of mosquito and house fly, antimalarial	[52, 53]
	tinjute	Ethiopia	Type 2 Diabetes Mellitus	[54]
	chiendog	Tigray, Ethiopia	ectoparasites in livestock	[55]
	chiendog	Tigray, Ethiopia	repellent of mosquitos	[47]
	tungut	Central Ethiopia	evil eye	[48]
		North Ethiopia	vomiting, nausea, diarrhea, dysentery	[46]
		North Ethiopia	sterilization, ritual custom	[56]
O. limbata	bui, phut kanda	Northwest Pakistan	treatment of children's gums and for ophthalmia in men, boils, wound, scabies	[57–59]
	pishkand	Battagram, Pakistan	jaundice	[60, 61]
	spin azghay	Malakand, Pakistan	dental problems, wounds, cuts, narcotic, tonic, anticancer and goiter	[62]
	bui	Punjab, Pakistan	treatment of children's gums and for opthalmia in man	[63]
	sassa	Chon. Karak, Pakistan	treatment of children's gums and for opthalmia in man	[61]
	chitta jand	Jhelum, Pakistan	acidity	[64]
	chittakanda	Azad Jammu and Kashmir, Pakistan	antiseptic, antibacterial, wound healing, ophthalmia, gum diseases	[65]
	spin azghay	Dir lower, Pakistan	hypertension	[66]
	jand	Azad Kashmir, Pakistan	used to improve eye vision	[67]
		Abottabad, Cherat, Mardan, Malakand, Kohat, Pakistan	antiulcer, antispasmodic, antidepressant, opthalmia and gums diseases	[68]
	koribooti	Himalaya	wound healing	[69]
O. persica	golder	Baluchistan, Iran	diabetes, rheumatism, cardiac distress, reducing palpitation, hypertension, laxative, carminative, antipyretic, cold, hyper lipidemia, gastric discomfort, parasite repellent, sedative, headache	[17]
O. tomentosa		North Ethiopia	ascariasis, diarrhea	[46]

Phytochemicals

Diterpenoids

Seventy-five diterpenes (▶ **Figs. 1–3**) were isolated and characterized both by their AP and roots of taxa of genus *Ballota* and *Otostegia,* and their presence is summarized in ▶ **Table 3** (labdane diterpenoids) and ▶ **Table 4** (other diterpenoids). Apart from 7*α*-acetoxyroyleanone (**73**) and coleon A (**74**), belonging to abietane diterpenoids, and 7,8*β*-epoxymomilactone-A (**75**), belonging to pimarane diterpenoids, 3 main carbon-skeletons occur: labdane, hispanane, and clerodane.

The labdane diterpenoids (**1–50**) (▶ **Figs. 1** and **2**) are characterized by some interesting structural features. They all belong to a normal labdane stereochemical series, although Gray et al. [118] claimed, based on the optical rotation, that compound **27** had an *ent*-labdane skeleton. The C-11-C-16 fragment, never carrying an oxygenated function on C-11 and C-12, can occur with different substructures. The most common one involves C-13/C-16 in a furane ring that, in a few cases, is oxidized to *γ*-lactone (**6, 7, 13–16, 32, 49**). In almost all of the remaining labdanes, C-13 is involved in the formation of a spiro structure including C-9. By NOE correlations between H-16 and Me-17, it has been shown that all of them belong to the 13*R* stereochemical series.

The decalin moiety contains some constant functional features: the decalin junction is always *trans* and the methyl groups (C-17) in position C-8; when it is not present, a C-8/C-9 double bond is always *α*-orientated. In the majority of the structures, C-6 and C-7 show oxygenated functions and methyl 18 is devoid of functionalization.

Hispanane-type diterpenoids (▶ **Fig. 3**) are a scarce group of natural diterpenoids that exhibits a 6/7/6 tricylic system featured with a 7-membered carbon ring.

To our knowledge, apart from hispaninic acid (**51**) and hispanonic acid (**52**), isolated from *B. hispanica* [104, 105], limbatenolides A (**54**), B (**55**), D (**57**), E (**58**) [107, 109], and limbetazulone (**53**) [106], isolated from *O. limbata* and limbatenolide C (**56**), isolated both from *O. limbata* [107] and *O. persica* [108], only 5 other natural hispananes have been characterized up until now: methyl verticoate (from *Sciadopitys verticillata* (Thunb.) Seibold & Zucc.) [119], salviatalin A [120], salviadigitoside A [120] and salviatalin A 19-*O*-*β*-glucoside [121] (from *Salvia digitaloides* Diels), and

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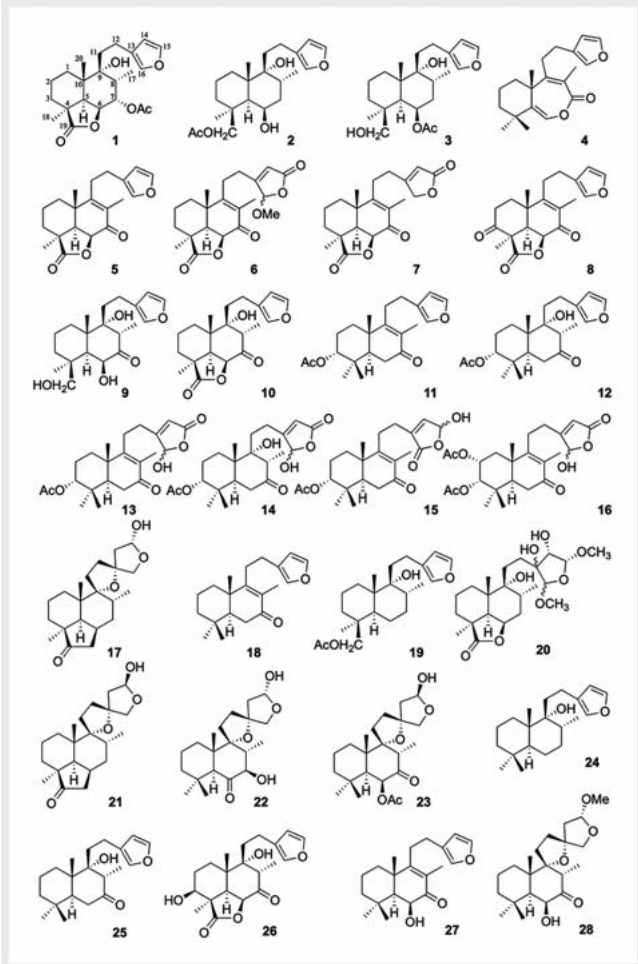
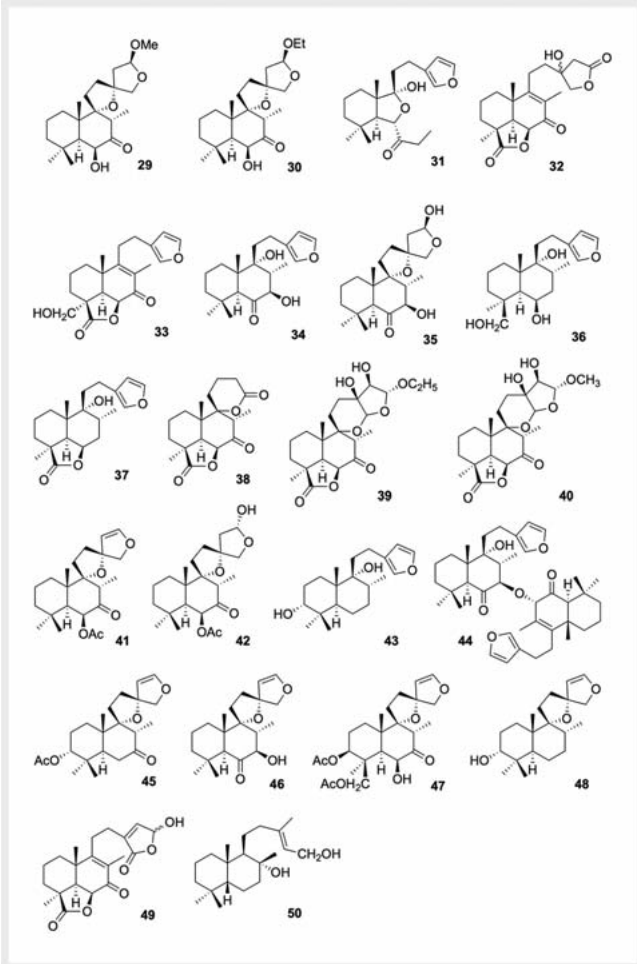


▶ **Fig. 1** Structures of ladbane diterpenes.



▶ **Fig. 2** Structures of ladbane diterpenes.

viburnumoside (from *Viburnum cylindricum* Buchanan-Hamilton ex D. Don) [122].

With the exception of viburnumoside, shown to have an *ent* absolute configuration (β-H 5 and α-CH_3 20) [122], the absolute configurations of any of the other hispananes have been not determined. In this review, we will report the configuration depicted in the original papers (α-H 5 and β-CH_3 20). The plausible biosynthetic pathway was speculated as a pimarane [121] or labdane way [123].

Clerodane diterpenods (▶ **Fig. 3**) showed, differently from labdanes, both a *trans* junction and a *cis* junction of the decalin moiety (**64–66**). Apart from ballodiolic acid (**62**) and ballodiolic acid A (**63**), all the other compounds showed the C-13/C-16 as furane ring (**67, 68**) or γ-lactone. Common features to all compounds are the absence of functionalizations at C-1, C-2, C-7, C-11, C-12, Me-17, Me-19, and Me-20 and the presence of a carboxylic acid on C-18 that, in some cases, is lactonized with the hydroxyl group on C-6 (**59, 61, 63, 64, 67–70**). In ▶ **Table 5**, all of the diterpenes are listed, according to their skeleton, in alphabetical order along with their ^{13}C NMR spectra, when available.

Flavonoids

In the extensive bibliographic search undertaken, a total of 91 different flavonoids were identified from 22 taxa belonging to *Ballota* genus and 3 taxa belonging to *Otostegia* genus.

The structures of the sugar and acyl groups occurring in the secondary metabolites are shown in ▶ **Fig. 4** and the formula of all compounds are depicted in ▶ **Figs. 5–10**. The reported compounds encompass flavones (23 compounds; ▶ **Fig. 5**), flavonols (13 compounds; ▶ **Fig. 6**), flavonoid glycosides (24 compounds; ▶ **Fig. 7**) flavonoid acyl derivatives (20 compounds; ▶ **Fig. 8**), *C*-glycosyl-flavonoids (4 compounds; ▶ **Fig. 9**), flavanones derivatives (4 compounds; ▶ **Fig. 10**), and flavanols (4 compounds; ▶ **Fig. 10**).

▶ **Tables 6–8** contain all the flavonoids with their semi-systematic or trivial names, and the genera and species, ordered alphabetically, from which the compounds have been isolated. The most common compounds are apigenin-7-*O*-β-D-glucopyranoside (**112**) (9 taxa), ladanein (**79**) (8 taxa), apigenin (**75**) (6 taxa), luteolin-7-*O*-β-D-glucopyranoside (**116**) (6 taxa), and rutin (**124**) (6 taxa).

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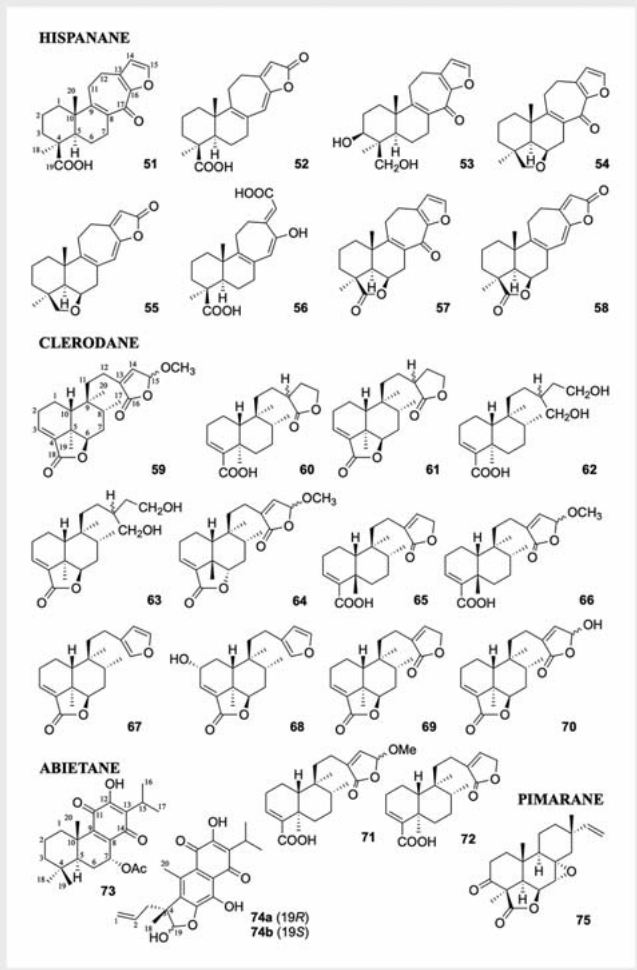

▶ **Fig. 3** Structures of hispanane, clerodane, abietane, and pimarane diterpenes.

Flavonoid glycosides, described in 24 reports, account for the vast majority of the 91 total flavonoid reports published so far, followed by flavones (23 reports). Flavonoid coumaroyl glycosides, present in 18 reports (compounds **136–141, 143–150, 152–155, 163**), have a peculiar chemotaxonomical significance and are generally considered valuable markers in the Labiatae family [137].

Although the majority of the flavonoids identified had already been detected in other genera of several families, some were identified for the first time.

From the AP of *Ballota acetabulosa,* 5 flavonoids were isolated (**112, 120, 138, 145**, and **146**). Compound **146** is a new natural flavonoid characterized as the *cis* isomer of chrysoeriol-7-*O*-*β*-(3′′-*p*-coumaroyl)glucopyranoside. The *trans* isomer **145** (co-occurring in the same species) was previously described from other species belonging to the Lamiaceae family [161].

The new flavonoid coumaroyl glucosides leufolins A (**163**) and B (**152**) were isolated from the EtOAc soluble fraction of the WPs of *L. urticifolia* (syn. *B. arabica*). Their structures were elucidated on the basis of extensive analysis of 1D and 2D NMR spectral data. Both compounds exhibited significant inhibitory potential against the enzyme butyrylcholinesterase. The unusual oxygenated pattern of the flavonoid moiety of leufolin B (**153**), devoid of hydroxyl group at C-5 [171], is noteworthy.

From the *n*-BuOH extract of the AP of *Panzeria alaschanica* Kuprian. (syn. *B. lanata* L.), 2 new flavone C-glycosides, named panzeroside A (**156**) and B (**157**), were isolated. The 2 new compounds demonstrated significant and dose-dependent analgesic and anti-inflammatory effects [173].

The MeOH extract of the roots of *O. limbata* was subjected to several chromatographic separations to give 4 new poly-glycosyl derivatives of kaempferol: compounds **135, 153, 154**, and **155**, the last 3 also carrying *p*-coumaroyl groups. Their rather complex structures were elucidated by extensive 1D and 2D NMR [167, 172].

Other metabolites

Apart from diterpenoids and flavonoids, several other metabolites have been identified in *Ballota* and *Otostegia* taxa: tritepenoids, steroids (▶ **Fig. 11**), carboxylic acids (▶ **Fig. 12**), carotenoids (▶ **Fig. 13**, **Table 9**), nitrogen containing compounds (▶ **Fig. 13**), phenylpropanoids, and miscellaneous (▶ **Fig. 14**, **Table 10**).

The first study on *Ballota* and *Otostegia* genera was carried out in 1911 by Piault [197], which isolated the tetrasaccharide stachyose from the roots of *B. nigra* subsp. *foetida* (**237**). The following report dates 1934 when, from the same species, Balansard isolated choline (**213**) and stachydrine (**217**) [191].

Phenylpropanoids (**218–227**) occur within 10 compounds and, apart from forsythoside B (**223**) and verbascoside (**227**), are present in several species. The main source of this class of compounds is *B. nigra* from which ballotetroside (**221**), a new derivative, was isolated [194].

Triterpenoids (10 compounds) and steroids (8 compounds) are represented by rather common metabolites, although there are some exceptions. For example, moronic acid (**173**) was isolated for the first time in *B. cinerea* [178], and the new steroid leucisterol (**179**), as well as the new peroxy acid urticic acid (**206**), were isolated from the chloroform soluble fraction of the WP of *B. arabica* (syn. *L. urticifolia*). Leucisterol (**179**) showed potent inhibitory activity against butyrylcholinesterase enzyme [181]. Recently, the new, structurally quite complex, bacteriohopane-type derivative **178** was isolated from *B. cinerea* (syn. *Roylea cinerea* (D. Don) Baill.) [182]. In the same work, the *β*-lactam cinerealactam E (**214**) [88] was also detected. Both compounds were shown to have a significant effect on the decline in blood glucose levels supporting the role of *B. cinerea* in Ayurvedic medicine for diabetes.

In ▶ **Table 11**, the occurrence of all of the metabolites in the single taxa is summarized. For some common compounds, whose structures have not been depicted in this review, the trivial name is reported.

EOs

The chemical composition of EOs obtained from 21 species among *Ballota* and *Otostegia* taxa has been investigated. They are mainly distributed in the Mediterranean area, whereas the *Otostegia* species are almost totally distributed in western Asia and *Ballota lanata*, syn. *Panzeria* (*Panzerina*) *lanata*, found in eastern Asia (Siberia and Mongolia). The major compounds (> 3%) occurring

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▶ **Table 3** Distribution of labdane diterpenes in *Ballota* and *Otostegia* taxa.

No	Names	Taxa
1	7α-acetoxymarrubiin	*B. nigra* [70]
2	6-acetyl-marrubenol	*B. deserti* [24]
3	19-acetyl-marrubenol	*B. deserti* [24]
4	balloaucherolide	*B. aucheri* [71]
5	ballonigrin	*B. acetabulosa, B. antalyensis, B. cristata, B. larendana, B. saxatilis* subsp. *brachyodonta* [72, 73], *B. aucheri* [74], *B. inaequidens* [72, 73, 75, 76], *B. lanata* [77], *B. nigra* [70], *B. nigra* subsp. *foetida* [72, 73, 78], *B. pseudodictamnus* [79], *B. rupestris* [70, 78], *B. saxatilis* [72, 73, 80], *B. undulata* [81], *O. fruticosa* [82]
6	ballonigrin lactone A	*O. limbata* [83]
7	ballonigrin lactone B	*O. limbata* [83]
8	ballonigrinone	*B. rupestris* [70, 78], *B. undulata* [81]
9	ballotenol	*B. nigra* subsp. *foetida* [84]
10	ballotinone	*B. aucheri* [71], *B. nigra* subsp. *foetida* [85], *B. undulata* [81]
11	calyenone	*B. cinerea* [86]
12	calyone	*B. cinerea* [86, 87]
13	cinereanoid A	*B. cinerea* [87]
14	cinereanoid B	*B. cinerea* [87]
15	cinereanoid C	*B. cinerea* [88]
16	cinereanoid D	*B. cinerea* [88]
17	cyllenin A	*B. deserti* [89, 90]
18	dehydrohispanolone (hispanone)	*B. acetabulosa, B. antalyensis, B. cristata, B. larendana, B. latibracteolata, B macrodonta, B. nigra* subsp. *uncinata, B. pseudodictamnus* subsp. *lycia, B. rotundifolia, B. saxatilis* subsp. *brachyodonta* [72, 73], *B. saxatilis* [72, 73, 80], *B. undulata* [81], *O. fruticosa* [82]
19	6-dehydroxy-19-acetyl-marrubenol	*B. deserti* [24]
20	desertin	*B. deserti* [89, 90]
21	15-*epi*-cyllenin A	*B. deserti* [89, 90]
22	15-*epi*-leopersin C	*O. fruticosa* [82]
23	15-*epi*-otostegin B	*O. fruticosa* [82]
24	16-epoxy-9-hydroxylabda-13(16), 14- diene	*B. deserti* [24]
25	hispanolone	*B. acetabulosa, B. cristata, B. pseudodictamnus* subsp. *lycia, B. rotundifolia, B. saxatilis* subsp. *brachyodonta* [72, 73], *B. africana* [91], *B. andreuzziana* [79], *B. hirsuta* [92], *B. inaequidens* [72, 73, 75, 76], *B. saxatilis* [72, 73, 80]
26	3β-hydroxyballotinone	*B. undulata* [81]
27	6β-hydroxy-15,16-epoxy-labda-8,13(16),14-trien-7-one	*B. aucheri* [74]
28	6β-hydroxy-15α-methoxy-9α,13,15,16-bis-epoxylabd-7-one	*B. aucheri* [71]
29	6β-hydroxy-15β-methoxy-9α,13,15,16-bis-epoxylabd-7-one	*B. aucheri* [71]
30	6β-hydroxy-15β-ethoxy-9α,13,15,16-bis-epoxylabd-7-one	*B. aucheri* [71]
31	9α-hydroxy-6,9 : 15,16-diepoxy-13(16),14-labdadien-7-one	*B. aucheri* [74]
32	13-hydroxyballonigrolide	*B. lanata* [77], *B. nigra* [93, 94]
33	18-hydroxyballonigrin	*B. acetabulosa* [95], *B. pseudodictamnus* [79], *B. saxatilis* [96]
34	leoheterin	*B. aucheri* [71, 74, 97], *O. fruticosa* [82, 98]
35	leopersin C	*O. fruticosa* [82]
36	marrubenol	*B. pseudodictamnus* [79]
37	marrubiin	*B. deserti* [89, 90], *B. nigra* subsp. *foetida* [85, 99]
38	marrulactone	*B. deserti* [89, 90]
39	marrulibacétal	*B. deserti* [89, 90]
40	marrulibacétal A	*B. deserti* [90]

continued

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▶ **Table 3** *Continued*

No	Names	Taxa
41	otostegin A	*O. fruticosa* [82]
42	otostegin B	*O. fruticosa* [82]
43	otostegindiol	*O. integrifolia* [100, 101]
44	persianone	*B. aucheri* [74]
45	precalyone	*B. cinerea* [86]
46	preleoheterin	*B. aucheri* [71, 97], *O. fruticosa* [82]
47	preleosibirin	*B. nigra* subsp. *foetida* [102]
48	preotostegindiol	*O. integrifolia* [100]
49	rupestralic acid	*B. rupestris* [103]
50	vulgarol	*O. fruticosa* [82]

in the chemical composition of the EOs are reported in ▶ **Table 12**.

All papers are quite recent, they have been published starting in 2002, except for one [224], published in 1995.

The first published paper concerns the analysis of an Egyptian *O. fruticosa* [224] species, cultivated in the station of faculty of agriculture of Mansoura University, containing mainly monoterpenes with a high level of thymol (43.7%). A recent re-investigation of the same species collected wild in the Sinai region showed a composition strongly dominated by sesquiterpenes with the caryophyllene oxide being the most abundant component (60.8%) [175].

For the single species *Ballota sechmenii* Gemici & Leblebici, only the relative content of linalool (5.0%) and its enantiomeric composition, (+)-isomer (26.9%), (−)-isomer (73.1%) have been determined [223]. No other component of the EO was reported.

With only a few exceptions, such as *B. lanata* [29, 206] and 2 *B. nigra* specimens collected in the Golestan region of Iran [210] and Ukraine [211], respectively, *Ballota* species EOs are mainly composed of sesquiterpenes with caryophyllene, caryophyllene oxide, and germacrene D often identified as main compounds. On the contrary, in *B. lanata,* monoterpenes are the dominant components, similar to the *B. nigra* of Golestan. The analysis of EOs of different plant parts of Ukrainian *B. nigra*, showed that fatty acids are the most relevant compounds with sesquiterpenes occurring only in the corallas. However, a nonconventional method of EO extraction was applied.

The *Otostegia* species studied to date shows controversial results. The case of the *O. fruticosa*, discussed above, and of the *O. michauxii*, collected in 2 different locations, are emblematic. In fact, the *O. michauxii* from southern Zagros of Iran show caryophyllene oxide as a main compound [225], whereas the one collected in the Fars province of Iran had an equal amount of monoterpenes and sesquiterpenes [226]. In *O. integrifolia*, the monoterpene α-pinene occurs in 31% of the oil [56], whereas in some collections of *O. persica*, in several places of southeast Iran, a clear trend cannot be observed.

Biological Properties

This section deals with the *corpus* of scientific evidence related to the claims of the biological effects of *Ballota* and *Otostegia* genus utilized in traditional medicine (▶ **Table 2**). The most widespread usage of the plants is as an aqueous infusion of the drug, which is normally made from the WP dried. The beneficial effects should normally be associated with the presence of polar or water-soluble active principles. Indeed, most of the cited literature deals with the effect of the extract obtained from leaves, stems, roots, flowers, WPs in polar solvent, such as EtOH, MeOH and water, as well as mixture of them. However, investigations concerning the bioactivity of fractions obtained with less polar solvents, such as choloroform, *n*-Hex, and EtOAc are also present. In some cases, isolated individual compounds were assessed for their bioactivity. In other cases, the EOs are the focus of the research and their composition is investigated and correlated to the bioactivity observed for that species.

In this report, a selection of the more relevant results, obtained with rigorous and well-defined methodological approaches, are taken into consideration. Redundant investigations that report data concerning the same combinations of plant species and biological targets can often be found in literature, in particular concerning antimicrobial activity.

Antioxidant activity

Many of the effects of *Ballota* and *Otostegia* reported in ▶ **Table 2** may be related by their general antioxidant activity, which is well documented in the literature. This activity is generally attributed to the presence of phenolic compounds that are ubiquitous in these genera. In a few cases, terpenoidic compounds, in particular diterpenes, were also identified as the source of antioxidative properties of the drug. The mechanisms of action may include oxygenated radicals scavenging, inhibition of the enzymatic peroxidation, etc. Furthermore, the variety of antioxidant activity evaluation protocols utilized often make it difficult to directly compare the effects of different species. Nevertheless, the antioxidant activity of many *Ballota* and *Otostegia* plants has been interestingly and undoubtedly demonstrated. These findings are summarized in ▶ **Table 13**, where for each investigation reviewed

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the species involved is reported together with its provenience, the extraction mode, and the testing procedure implemented.

As it can be inferred from the analysis of ▶ **Table 13**, *B. nigra* and *O. persica* are the most studied species. Their antioxidant activity was evaluated in the EO [196, 228, 229], as well as in different polarity fractions (extraction solvents: PE, Ac, EtOAc, MeOH, EtOH, water) of the extract obtained from leaves, AP, and the WP. In some cases, a number of individual active compounds were isolated and identified. The following were purified from leaf extract (water/EtOH 1 : 1) of *B. nigra* collected in France [236, 237]: (+)-(*E*)-caffeoyl-L-malic acid (**186**), verbascoside (**227**), forsythoside B (**223**), arenarioside (**220**), and ballotetroside (**221**). On the other hand, morin (**110**) and quercetin (**100**) were isolated from the bio-guided purification of the methanolic extract of *O. persica* [160]. In an interesting study [236], some chemical indicators of the intracellular inflammatory cascade reaction of the neutrophils were evaluated: superoxide anion, H_2O_2, HClO, and OH radical. All of the compounds were found to be active, inhibiting the development of oxygenated species to various degrees; only ballotertoside (**221**) was inactive in the superoxide anion and OH radical tests. In another study [237], the same authors evaluated all 5 molecules for their inhibitory efficacy with respect to the oxidation of low-density lipoproteins (LDL). They were also assessed for their Cu(II) chelating power, as this is the well-known mechanism of action of the antioxidant quercetin. None of them were able to behave as a copper chelating agent. The infusion of *B. nigra* leaves from the Czech Republic was shown to possess outstanding antioxidant activity, in particular by DPPH, NO, and superoxide anion scavenging ability [185]. On the contrary, no OH radical scavenging ability was revealed. In terms of organic acids and polyphenol content of the infusion, the composition was determined by HPLC/DAD and HPLC/UV analysis and the authors inferred the correlation between these compounds and the observed antioxidant activity. The crude methanolic extract of AP of *B. hirsuta* [234] and *O. limbata* [241] were further partitioned in several solvents in order to select phenolic enriched subfractions following the solubility properties of different compounds, the EtOAc fraction being the most active in both cases: in the DPPH test, the IC_{50} were 13.53 µg/mL for *O. limbata* and 70.0 µg/mL for *B. hirsuta*. On the contrary, the less active fraction of the extract was the one in H_2O for *B. nigra* (129.5 µg/mL) and the one obtained in $CHCl_3$ for *B. hirsuta* (260 µg/mL). A significant difference in the antioxidant power of different solvent fractions was found for *O. persica* collected in Iran [158]. The fraction soluble in MeOH showed LPO inhibition in the NH_4SCN test comparable to that of α-tocopherol (95.87 %). On the other hand, the fractions soluble in *n*-Hex and $CHCl_3$ were poorly active (2.5 and 1.9 %, respectively). These variations in the antioxidant activity, evidenced by different partition solvents, can be related to the affinity of the active metabolites (poly-phenols and flavonoids) to these solvents.

The relation between the antioxidant power of *O. persica* extract (AP, 70 % MeOH) and the protective effect against the damages caused by the oxidative stress on the endothelium cells, was investigated *in vitro* on a human cell line: the umbilical vein endothelial cells [244]. No toxicity was revealed up to 250 µg/mL of extract. The oxidative effects were induced by H_2O_2 and evaluated by the cell viability essay (MTT), intracellular and extracellular total peroxides test, and FRAP. The extract significantly reduced the effect of H_2O_2 in a dose-dependent fashion (50–250 µg/mL).

▶ **Table 4** Distribution of other diterpenes in *Ballota* and *Otostegia* taxa.

	Hispanane skeleton	
51	hispaninic acid[a]	*B. hispanica* [104, 105]
52	hispanonic acid[a]	*B. hispanica* [104, 105]
53	limbetazulone	*O. limbata* [106]
54	limbatenolide A	*O. limbata* [107]
55	limbatenolide B	*O. limbata* [107]
56	limbatenolide C	*O. limbata* [107], *O. persica* [108]
57	limbatenolide D	*O. limbata* [109]
58	limbatenolide E	*O. limbata* [109]
	Clerodane skeleton	
59	ballatenolide A	*O. limbata* [107], *O. persica* [108]
60	ballotenic acid	*O. limbata* [110]
61	ballotenic acid A	*O. limbata* [111]
62	ballodiolic acid	*O. limbata* [110]
63	ballodiolic acid A	*O. limbata* [111]
64	limbatolide A	*O. limbata* [112]
65	limbatolide B	*O. limbata* [112]
66	limbatolide C	*O. limbata* [112]
67	limbatolide D	*O. limbata* [113]
68	limbatolide E	*O. limbata* [113]
69	limbatolide F	*O. limbata* [114]
70	limbatolide G	*O. limbata* [114]
71	15-methoxypatagonic acid	*O. limbata* [107], *O. persica* [108]
72	patagonic acid	*O. limbata* [107], *O. persica* [108]
	Abietane skeleton	
73	7α-acetoxyroyleanone	*B. nigra* [115]
74	coleon A	*B. cinerea* [116]
	Pimarane skeleton	
75	7,8β-epoxymomilactone-A	*B. arabica* [117]

The direct correlation between the phenolic compounds content is rather general, although some exceptions are also known. For example, in an investigation of the antioxidant properties of *O. limbata* from Pakistan [242], the methanolic extract was subsequently divided in fractions soluble in *n*-Hex, $CHCl_3$, EtOAc, *n*-BuOH, MeOH, and H_2O, and total content in phenolic compounds and flavonoids was determined. The EtOAc fraction resulted the one with the highest antioxidant power (EC_{50} TPPH test 60.9 µg, total phenolic compounds 1119 mg), even if the higher phenols content was found in *n*-Hex (3908 mg, EC_{50} 226.1 µg) and 1-butanol (3037 mg, EC_{50} 96.3 µg).

The antioxidant activity of apigenin-7-O-(6″-*O*-[*E*]-coumaroyl)-β-glucopyranoside (**139**), a flavonoid glycoside isolated from the *B. lanata* (syn. *P. alaschanica*) AP collected in China [169], was determined *in vivo* by evaluating its lipid peroxidation inhibitory activity. A diabetes mellitus–related oxidative stress was induced in

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▶ **Table 5** ^{13}CNMR data of diterpenes from *Ballota* and *Otostegia* taxa.

	Skeleton numbering	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	1′	2′	Ref.
	Labdane skeleton																							
1	7α-acetoxy-marrubiin	33.4	17.5	29.3	43.7	46.0	75.8	70.6	38.8	79.2	39.1	28.4	18.4	124.6	110.7	138.8	143.2	13.9	22.8	183.1	22.6	171.0	21.0	[70]
2	6-acetyl-marrubenol	Not reported in literature																						
3	19-acetyl-marrubenol	Not reported in literature																						
4	balloaucherolide	37.2	17.2	32.3	35.7	124.3	143.1	181.7	140.5	165.8	43.8	23.8	29.4	127.4	110.5	140.5	143.1	11.6	28.1	27.9	27.6			[71]
5	ballonigrin	30.3	17.8	27.7	42.0	49.5	75.5	193.2	131.2	166.7	36.7	30.0	24.6	123.7	110.5	143.1	138.8	11.9	24.5	180.1	28.0			[81]
6	ballonigrin lactone A	28.1	21.9	27.6	42.2	49.3	78.8	194.1	135.7	165.3	39.1	29.9	24.6	139.1	141.3	100.9	170.6	17.4	26.7	176.4	22.4	56.2		[83]
7	ballonigrin lactone B	26.1	21.3	28.2	45.9	48.3	80.1	197.1	132.7	162.4	38.5	31.2	22.9	136.5	145.9	74.4	172.1	17.6	27.1	178.5	23.1			[83]
8	ballonigrinone	30.1	34.0	203.4	52.1	50.2	74.5	191.3	132.6	163.7	36.1	30.3	24.1	123.4	110.5	143.3	138.8	12.1	21.6	172.1	24.2			[81]
9	ballotenol	35.5	18.9	39.3	44.2	51.4	74.9	213.0	46.0	82.9	40.1	43.5	22.0	126.0	111.4	143.3	138.8	8.7	27.8	67.0	20.1			[84]
10	ballotinone	28.8	17.8	28.8	41.6	44.6	75.6	209.4	51.4	77.7	40.6	37.8	18.1	124.2	110.6	143.1	138.7	15.7	26.3	180.3	17.9			[81]
11	calyenone	34.5	22.9	76.8	36.6	44.5	30.1	199.3	166.1	130.6	40.4	29.4	24.3	124,3	110.5	142.3	138.6	18.0	27.0	21.3	11.5	170.2	21.1	[86]
12	calyone	25.6	22.7	77.3	37.0	41.1	38.5	211.4	51.0	81.6	43.0	34.7	21.5	124.6	110.6	143.1	138.5	8.3	27.6	21.2	16.0	170.6	21.5	[87]
13	cinereanoid A	30.4	23.8	78.5	37.7	46.2	35.5	201.9	131.9	168.3	42.1	27.8	27.6	176.3	118.2	173.6	100.9	11.6	27.6	21.7	18.2	172.3	21.1	[87]
14	cinereanoid B	26.8	23.8	79.2	38.1	42.3	39.5	214.5	51.9	82.5	44.5	32.3	25.6	172.6	117.8	173.7	101.2	8.6	28.2	21.9	16.8	172.6	21.1	[87]
15	cinereanoid C	30.4	23.8	78.5	37.7	46.2	35.5	202.0	132.0	168.5	42.1	25.6	28.5	137.4	147.0	99.2	173.8	11.8	27.6	21.8	18.2	172.4	21.1	[88]
16	cinereanoid D	35.5	69.2	77.6	38.9	45.6	35.2	201.3	132.3	166.8	43.0	27.5	27.5	170.9	118.4	173.4	100.9	11.7	27.8	21.4	19.4	172.1	21.1	[88]
17	cyllenin A	28.4	17.3	27.6	43.6	45.8	75.7	30.9	31.2	91.3	38.5	29.1	34.7	89.5	46.0	98.7	76.1	16.9	22.6	183.6	23.0			[124]
18	dehydrohispano-lone (hispanone)	35.8	18.6	41.3	33.1	50.2	35.2	200.3	130.3	167.0	40.9	30.2	24.2	124.5	110.5	143.0	138.6	11.4	32.5	21.3	18.1			[125]
19	6-dehydroxy-19-acetyl-marrubenol	31.6	18.2	35.7	36.9	47.5	22.6	31.2	36.6	79.6	43.0	35.0	22.6	125.5	110.8	142.8	138.4	16.2	26.8	67.1	16.9	171.4	20.9	[24]
20	desertin	28.4	18.2	28.3	43.9	45.0	76.3	31.6	32.5	75.3	40.1	28.2	27.4	81.2	80.2	110.8	108.6	16.8	23.0	183.9	22.2	56.4	55.1	[89]
21	15-*epi*-cyllenin A	28.3	17.5	27.7	43.6	45.8	75.7	30.9	31.2	90.0	38.4	28.9	37.2	89.5	48.1	98.7	76.4	16.9	22.4	183.3	23.2			[124]
22	15-*epi*-leopersin C	32.7	18.3	42.4	32.4	57.2	212.0	77.4	47.0	93.4	48.3	29.5	38.8	91.0	47.9	99.0	78.4	13.3	22.2	32.4	19.7			[126]
23	15-*epi*-otostegin B	34.8	19.1	44.1	35.2	49.1	76.0	204.5	45.5	98.2	43.9	30.1	38.8	90.6	42.1	101.2	71.0	9.5	33.1	24.9	20.3	169.8	21.8	[82]

cont.

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▶ **Table 5** *Continued*

	Skeleton numbering	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	1′	2′	Ref.
24	16-epoxy-9-hydroxylabda-13(16), 14- diene	Not reported in literature																						
25	hispanolone	31.9	18.5	41.3	33.6	46.4	39.2	211.9	50.9	81.8	43.3	34.7	21.5	124.8	110.7	143.0	138.6	8.2	33.1	21.4	16.2			[127]
26	3β-hydroxyballotinone	27.8	28.2	73.5	44.1	49.9	75.9	208.3	51.6	77.5	40.8	37.8	18.0	124.0	110.5	143.3	138.8	15.8	23.2	180.0	17.7			[81]
27	6β-hydroxy-15,16-epoxy-labda-8,13(16),14-trien-7-one	37.4	18.6	43.2	33.9	53.2	70.7	199.4	128.2	169.8	41.1	30.6	24.2	124.3	110.4	142.9	138.5	11.6	32.4	23.9	18.6			[74]
28	6β-hydroxy-15α-methoxy-9α,13,15,16-bis-epoxylabd-7-one	Not reported in literature																						
29	6β-hydroxy-15β-methoxy-9α,13,15,16-bis-epoxylabd-7-one	Not reported in literature																						
30	6β-hydroxy-15β-ethoxy-9α,13,15,16-bis-epoxylabd-7-one	Not reported in literature																						
31	9α-hydroxy-6,9:15,16-di-epoxy-13(16),14-labdadien-7-one	31.8	19.3	41.3	32.3	55.6	81.8	214.8	32.4	108.0	48.9	36.0	18.7	124.8	110.8	142.8	138.6	7.5	33.8	22.0	16.8			[74]
32	13-hydroxyballonigrolide	30.2	18.1	28.1	42.1	49.3	76.1	193.6	131.1	167.1	37.0	24.3	37.5	76.4	42.5	180.2	79.1	24.5	27.9	180.9	12.1			[77]
33	18-hydroxyballonigrin	30.2	17.7	22.5	48.8	45.6	77.3	193.5	131.2	166.6	36.4	29.4	24.2	123.8	110.6	143.2	138.8	29.0	67.5	180.1	12.1			[95]
34	leoheterin	31.6	18.1	42.0	32.2	55.9	212.0	77.1	47.6	77.2	49.0	34.2	21.2	124.7	110.6	143.2	138.6	12.4	32.6	22.2	18.0			[74]
35	leopersin C	32.3	18.2	42.4	32.4	57.0	211.5	77.4	46.8	92.1	48.2	29.1	35.9	90.7	46.4	99.0	76.9	13.1	22.1	32.4	19.7			[126]
36	marrubenol	33.8	18.5	40.7	38.9	49.3	65.9	38.9	31.1	77.0	43.4	34.9	21.5	125.4	110.8	142.8	138.5	16.2	27.8	69.1	19.6			[128]
37	marrubiin	35.1	18.1	28.5	43.8	44.8	76.3	31.4	32.3	75.6	39.7	28.3	21.0	125.1	110.7	142.9	138.5	16.6	22.9	184.0	22.3			[85]
38	marrulactone	28.8	18.4	28.5	44.1	45.0	75.7	31.7	32.4	88.3	39.0	34.5	20.5	34.4	172.1			16.8	23.1	183.4	22.6			[129]
39	marrulibacétal	27.9	17.9	28.2	43.9	44.7	76.5	32.3	33.7	80.4	41.0	21.1	29.6	75.6	78.5	108.7	105.4	19.5	23.2	183.9	22.0	63.9	15.0	[129]
40	marrulibacétal A	27.8	17.9	28.2	43.9	44.6	76.6	32.3	33.5	80.3	40.9	20.7	30.0	75.8	78.6	109.8	105.7	19.4	23.2	184.1	22.0	55.5		[90]
41	otostegin A	34.4	28.7	43.7	34.9	50.2	77.1	204.2	46.7	96.6	43.1	30.4	37.6	93.7	106.9	148.2	80.5	9.2	32.6	23.9	29.4	269.4	21.3	[82]
42	otostegin B	34.9	19.1	44.3	35.2	49.3	76.1	204.5	45.8	98.1	43.8	30.4	38.9	90.7	42.2	101.2	71.0	9.5	33.1	24.2	20.3	169.8	21.8	[82]
43	otostegindiol	25.1	25.6	76.3	43.2	39.8	21.6	31.4	37.1	77.5	37.8	35.5	21.9	126.1	111.3	143.2	138.9	16.5	22.6	29.0	16.8			[130]

cont.

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▶ **Table 5** *Continued*

	Skeleton numbering	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	1′	2′	Ref.
44	persianone	31.5	18.2	42.3	32.3	57.4	210.7	65.0	50.5	77.0	48.7	43.6	21,5	124.9	110.7	143.0	138.6	13.1	32.7	22.3	18.0			[74]
		36.5	18.7	42.2	32.1	58.3	211.3	67.9	128.1	144.4	45.1	29.2	25.4	125.1	110.7	142.8	138.5	16.5	33.1	21.9	21.3			
45	precalyone	38.2	22.7	77.5	36.9	40.1	38,2	210.2	50.0	86.0	42.5	29.4	26.4	94.0	107.0	148.3	80.8	17.1	27.1	21.2	9.2	170.3	21.1	[86]
46	preleoheterin	42.2	18.3	32.3	32.4	57.1	212.1	77.2	47.5	93.9	48.1	29.9	37.7	92.1	107.3	148.3	80.9	13.2	32.3	22.3	19.3			[71]
47	preleosibirin	Not reported in literature																						
48	preotostegindiol	25.1	25.2	76.1	42.4	39.8	21.2	31.6	37.3	93.3	37.7	32.0	35.6	93.0	107.6	147.8	81.5	17.6	22.4	29.5	21.1			[130]
49	rupestralic acid	30.1	18.1	28.1	42.3	49.4	76.1	193.8	131.7	165.6	36.9	24.7	27.3	136.0	146.5	98.5	172.1	24.7	27.4	180.7	12.1			[77]
50	vulgarol	36.8	19.0	42.6	33.3	46.9	21.0	37.8	74.0	61.2	39.2	25.8	43.4	140.9	123.4	59.5	16.9	32.3	33.5	21.7	25.2			[82]
	Hispanane skeleton																							
51	hispaninic acid[a]	36.7	19.4	37.4	43.8	52.9	20.7	34.1	126.2	147.9	40.8	25.0	27.0	151.2	113.6	169.4	158.1	116.5	28.3	177.4	16.9	51.2		[131]
52	hispanonic acid[a]	36.3	19.4	37.4	43.8	53.0	20.1	28.1	134.7	154.0	41.3	27.6	25.0	135.7	112.7	145.8	149.6	183.1	28.2	177.7	16.7	51.2		[131]
53	limbetazulone	34.3	27.5	80.1	42.8	52.2	18.2	27.9	134.3	154.3	40.2	25.1	28.0	135.8	112.8	146.0	149.6	183.1	22.5	64.1	29.9			[106]
54	limbatenolide A	34.2	18.1	27.5	42.8	51.1	80.1	28.0	134.2	154.1	40.1	25.0	27.9	135.6	112.7	145.9	149.1	183.0	22.5	64.1	19.9			[107]
55	limbatenolide B	34.5	18.6	29.6	42.7	51.1	80.1	33.8	125.7	147.9	39.0	24.7	27.0	151.0	113.7	172.0	157.9	116.1	22.4	64.0	20.2			[107]
56	limbatenolide C	37.2	19.5	36.0	43.5	53.0	20.8	35.6	127.5	142.4	40.5	25.2	27.8	130.1	115.1	172.9	143.2	114.9	28.1	182.2	17.2			[107]
57	limbatenolide D	38.4	20.4	32.4	44.1	53.1	83.5	29.2	136.1	152.6	42.3	25.4	28.6	135.9	113.4	144.1	150.6	184.3	25,2	180.1	18.5			[109]
58	limbatenolide E	37.1	20.9	33.0	42.6	51.9	80.3	35.6	127.1	145.9	40.3	24.8	27.2	250.1	114.1	170.6	156.7	118.2	27.0	181.9	19.3			[109]
	Clerodane skeleton																							
59	ballatenolide A	17.5	27.3	130.1	139.7	39.1	86.1	31.4	38.1	42.3	44.9	36.4	19.9	138.8	141.6	102.5	172.0	15.5	171.0	16.1	19.7	57.1		[107]
60	ballotenic acid	17.4	27.4	140.5	141.1	37.5	35.7	27.2	36.1	38.7	46.5	36.0	22.6	39.6	29.6	66.4	172.8	15.9	171.0	20.5	18.3			[110]
61	ballotenic acid A	17.8	28.1	134.2	140.1	40.1	84.5	30.9	39.3	42.5	45.7	35.9	23.6	41.2	32.3	70.1	173.2	16.5	172.7	17.8	20.6			[111]
62	ballodiolic acid	17.5	27.4	140.0	141.3	37.5	35.6	27.2	36.1	38.6	46.6	35.8	24.9	39.8	29.7	66.3	61.1	15.9	172.0	20.5	18.4			[110]
63	ballodiolic acid A	18.5	26.4	132.6	138.9	41.1	85.3	32.7	37.5	43.2	46.1	37.3	25.9	40.1	30.5	68.8	63.6	15.5	171.3	16.5	18.1			[111]
64	limbatolide A	19.4	28.5	132.1	140.3	40.5	85.2	30.3	37.5	40.9	45.6	37.8	21.3	139.7	142.3	100.8	173.6	15.9	170.8	31.7	22.5	55.7		[112]
65	limbatolide B	18.2	28.3	142.1	139.5	38.2	36.1	27.2	37.1	39.9	45.2	35.7	20.3	133.3	142.3	103.4	173.1	16.3	171.8	32.3	23.1	57.6		[112]
66	limbatolide C	18.1	27.3	142.3	139.1	38.5	36.0	26.5	38.3	40.1	45.4	36.9	21.3	136.1	144.4	71.4	173.7	16.8	171.5	33.1	16.8			[112]
67	limbatolide D	18.2	27.1	132.6	140.5	40.6	82.4	32.6	39.1	41.3	45.1	38.2	18.4	131.5	111.3	143.4	137.7	16.6	174.1	18.1	19.3			[113]
68	limbatolide E	30.5	72.3	125.6	139.6	42.3	84.5	33.1	40.5	44.3	46.7	37.1	20.1	130.1	111.7	143.6	140.2	15.8	172.1	19.3	19.8			[113]
69	limbatolide F	20.3	27.4	131.1	140.1	43.0	84.4	32.7	37.5	41.6	47.1	36.6	19.6	133.4	143.4	71.4	173.0	15.8	170.4	18.2	19.0			[114]
70	limbatolide G	19.5	28.3	133.9	141.2	42.4	83.4	33.8	39.3	40.1	46.2	37.8	18.0	135.6	141.4	101.1	171.8	16.1	169.3	17.5	19.5			[114]

cont.

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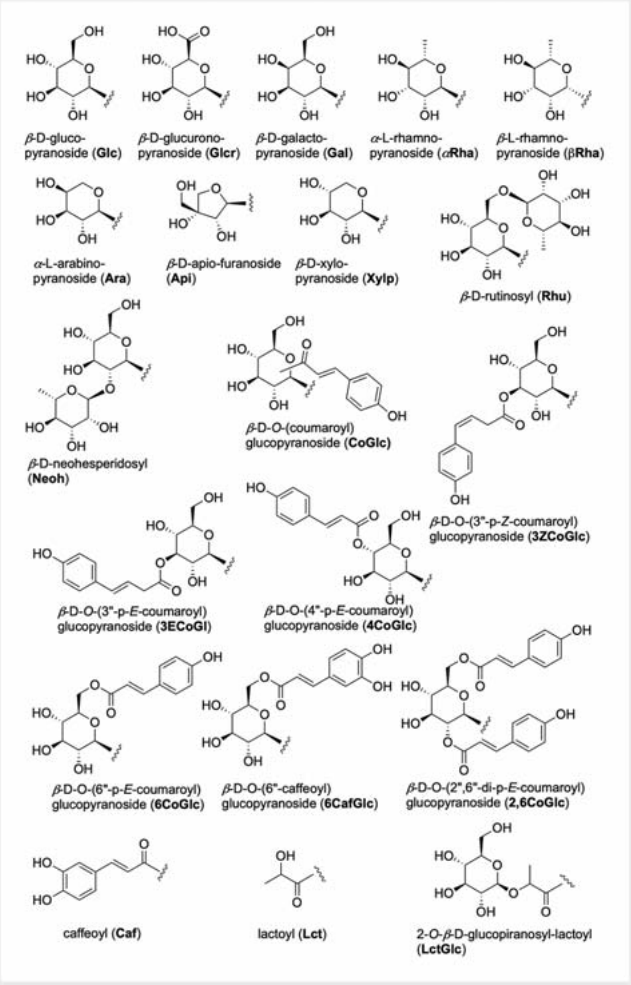
▶ **Table 5** *Continued*

	Skeleton numbering	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	1′	2′	Ref.
71	15-methoxy-patagonic acid	17.4	27.2	141.3	140.4	37.5	35.7	27.4	36.3	38.8	46.7	36.3	19.3	134.0	143.0	102.5	172.2	15.5	171.3	20.5	18.1	57.0		[107]
72	patagonic acid	17.3	27.4	141.2	140.4	37.5	35.7	27.2	36.2	38.7	46.6	36.2	19.2	134.9	143.5	70.2	174.3	15.9	172.5	20.5	18.2			[107]
	Abietane skeleton																							
73	7α-acetoxy-royleanone	35.8	18.8	41.0	33.0	46.1	24.6	64.5	139.4	149.9	39.1	183.7	150.7	124.7	185.4	24.1	19.7	19.9	21.6	33.0	18.5	169.5	21.1	[132]
74a	coleon A(19R)	119.5	132.5	43.0	50.4	137.0	152.4	146.9	116.8	120.3	134.4	180.6	154.5	125.4	191.2	23.9	19.8	19.8	18.4	107.1	17.4			[133]
74b	coleon A(19S)	118.4	135.1	38.5	50.0	136.9	152.1	146.9	116.8	120.2	134.3	180.6	154.5	125.5	191.2	23.9	19.8	19.8	24.6	110.5	17.6			[133]
	Pimarane skeleton																							
75	7,8β-epoxy-momilactone-A	Not reported in literature																						

[a]The spectra were recorded as methyl ester derivative.



▶ **Fig. 4** Structures of sugars and acyl moieties.

rats with a 7 week treatment of STZ. Afterward, the plasma concentration of malondialdehyde (MDA), co-enzyme Q_9, α- and γ-tocopherol were measured. A normalization in MDA values was observed in animals treated with 60 mg/kg b.w. of compound **139**, while the Q_9 and γ-tocopherol level remained comparable with those of negative controls.

Anti-inflammatory activity

This is mainly attributed to the presence of flavonoids and tannins in both genera. The bioactivity is generally evaluated in *in vivo* models. The aqueous extract of *Ballota glandulosissima* Hub.-Mor. & Patzak leaves collected in Turkey [245] administrated to rats with carrageenan-induced paw edema (100 mg/kg b.w.) was able to induce a significant reduction of the edema volume (32%). The aerial part aqueous extract of *Ballota inaequidens* Hub.-Mor. & Patzak from Turkey [246] showed similar effects by reducing paw edema in rats in a dose-dependent manner: the volume reduction coefficient ranged from 58 to 86% by administrating 50 to 200 mg/kg b.w. per day of extract. This species also showed significant, positive dose-dependent results in the abdominal stretching test in mice: 44–91% reduction by administrating 30–100 mg/kg b.w. per day of dry extract. A relevant anti-inflamma-

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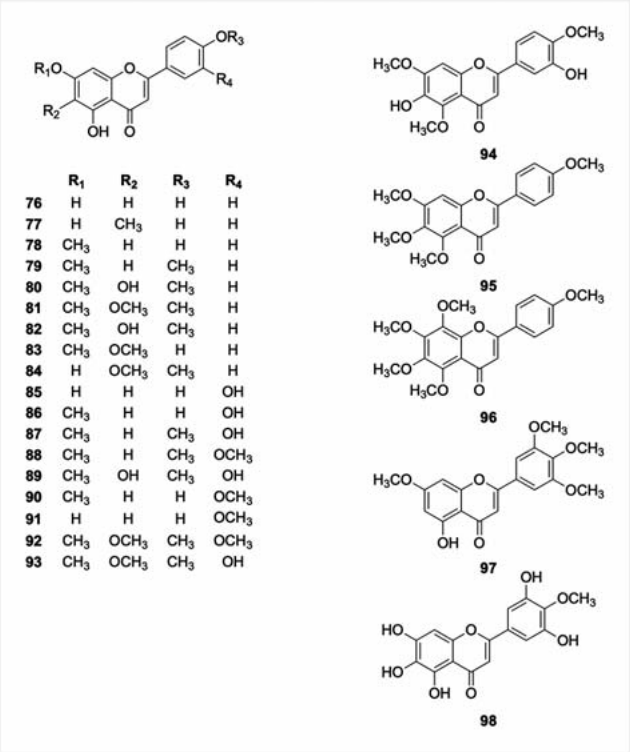
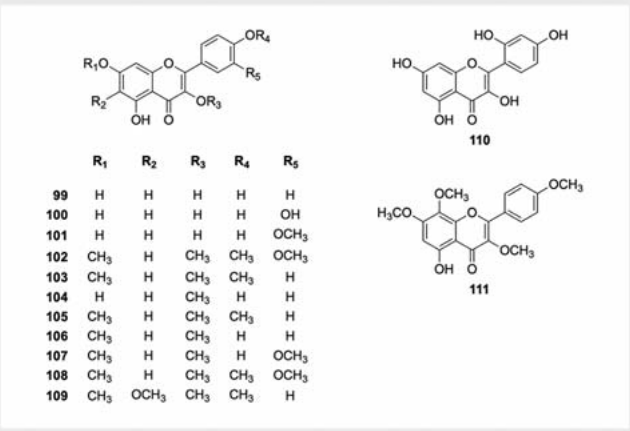


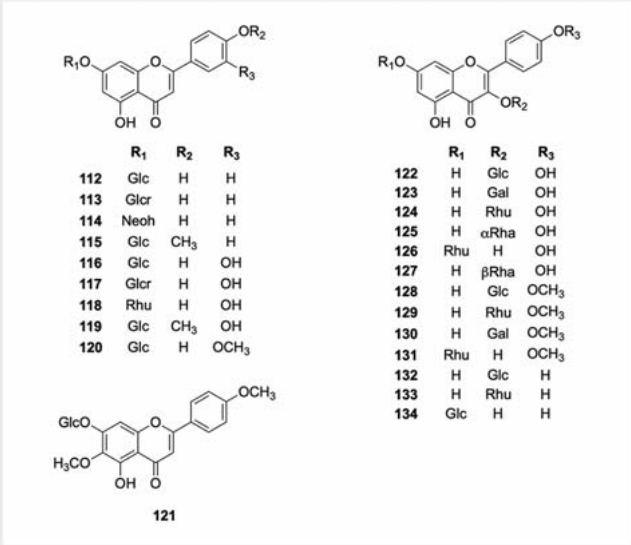
	R_1	R_2	R_3	R_4
76	H	H	H	H
77	H	CH_3	H	H
78	CH_3	H	H	H
79	CH_3	H	CH_3	H
80	CH_3	OH	CH_3	H
81	CH_3	OCH_3	CH_3	H
82	CH_3	OH	CH_3	H
83	CH_3	OCH_3	H	H
84	H	OCH_3	CH_3	H
85	H	H	H	OH
86	CH_3	H	H	OH
87	CH_3	H	CH_3	OH
88	CH_3	H	CH_3	OCH_3
89	CH_3	OH	CH_3	OH
90	CH_3	H	H	OCH_3
91	H	H	H	OCH_3
92	CH_3	OCH_3	CH_3	OCH_3
93	CH_3	OCH_3	CH_3	OH

▶ **Fig. 5** Structures of flavones.



	R_1	R_2	R_3	R_4	R_5
99	H	H	H	H	H
100	H	H	H	H	OH
101	H	H	H	H	OCH_3
102	CH_3	H	CH_3	CH_3	OCH_3
103	CH_3	H	CH_3	CH_3	H
104	H	H	CH_3	H	H
105	CH_3	H	CH_3	CH_3	H
106	CH_3	H	CH_3	H	H
107	CH_3	H	CH_3	H	OCH_3
108	CH_3	H	CH_3	CH_3	OCH_3
109	CH_3	OCH_3	CH_3	CH_3	H

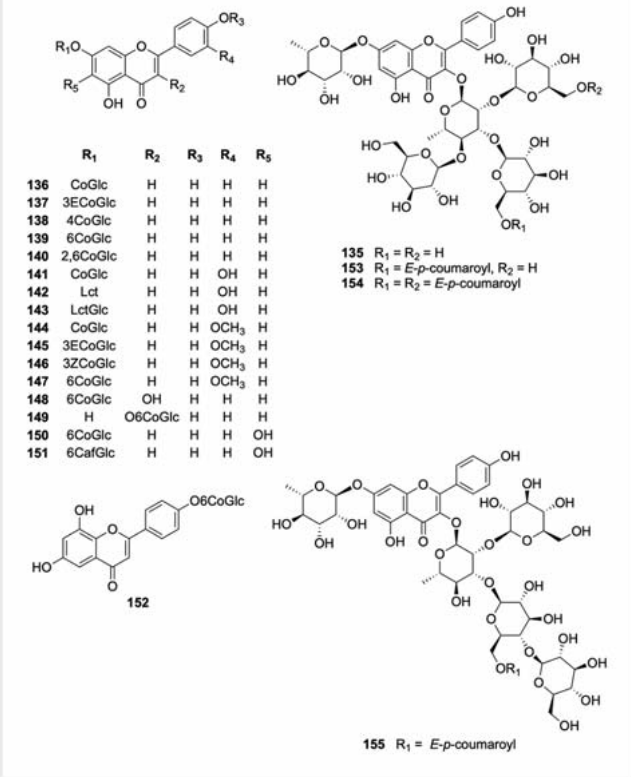
▶ **Fig. 6** Structures of flavonols.



	R_1	R_2	R_3
112	Glc	H	H
113	Glcr	H	H
114	Neoh	H	H
115	Glc	CH_3	H
116	Glc	H	OH
117	Glcr	H	OH
118	Rhu	H	OH
119	Glc	CH_3	OH
120	Glc	H	OCH_3

	R_1	R_2	R_3
122	H	Glc	OH
123	H	Gal	OH
124	H	Rhu	OH
125	H	αRha	OH
126	Rhu	H	OH
127	H	βRha	OH
128	H	Glc	OCH_3
129	H	Rhu	OCH_3
130	H	Gal	OCH_3
131	Rhu	H	OCH_3
132	H	Glc	H
133	H	Rhu	H
134	Glc	H	H

▶ **Fig. 7** Structures of glycosyl flavonoids.



	R_1	R_2	R_3	R_4	R_5
136	CoGlc	H	H	H	H
137	3ECoGlc	H	H	H	H
138	4CoGlc	H	H	H	H
139	6CoGlc	H	H	H	H
140	2,6CoGlc	H	H	H	H
141	CoGlc	H	H	OH	H
142	Lct	H	H	OH	H
143	LctGlc	H	H	OH	H
144	CoGlc	H	H	OCH_3	H
145	3ECoGlc	H	H	OCH_3	H
146	3ZCoGlc	H	H	OCH_3	H
147	6CoGlc	H	H	OCH_3	H
148	6CoGlc	OH	H	H	H
149	H	O6CoGlc	H	H	H
150	6CoGlc	H	H	H	OH
151	6CafGlc	H	H	H	OH

▶ **Fig. 8** Structures of acyl flavonoids.

tory activity was also demonstrated in the methanolic extract of the AP of *B. pseudodictamnus*. This species is included in a comparative study on the anti-inflammatory activity of endemic flora from Libya [247]. In the mice paw edema test, a single dose of 500 mg/kg b.w. reduced the edema volume by 51%.

The same animal model was employed in the evaluation of the anti-inflammatory activity of the crude extract of the aerial part of *O. persica* [166], as well as the fractions soluble in organic solvents of different polarities (PE, $CHCl_3$, EtOAc, *n*-BuOH, MeOH). The analgesic activities were also investigated. Both the fraction in BuOH and in MeOH were able to reduce the edema volume, the last one showing an efficacy comparable to that of indomethacin. Furthermore, the MeOH fraction showed analgesic activity with EC_{50} of 85.9 mg/kg b.w. Two active compounds were isolated from the methanolic fraction: vicenin-2 (**159**) and isorhamnetin-3-*O*-*β*-D-glucopyranoside (**128**).

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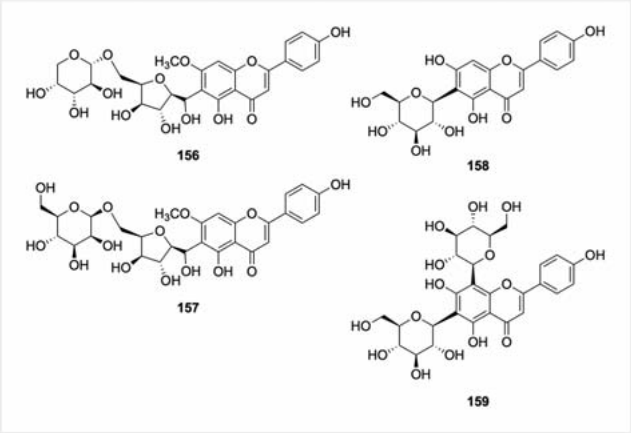
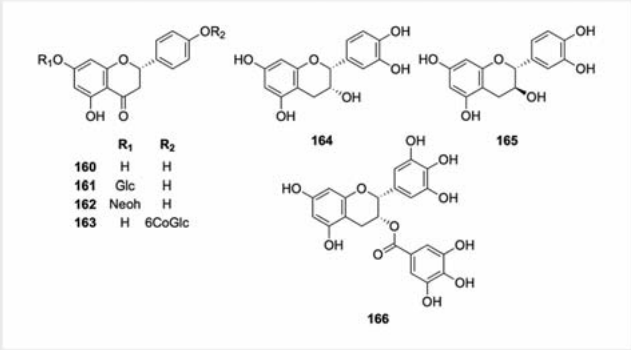


▶ **Fig. 9** Structures of C-glycosyl flavones.



▶ **Fig. 10** Structures of flavanones and flavanols.

The extract of *B. deserti* (Algeria) was obtained from AP with PE, dichloromethane, and MeOH. Their anti-inflammatory activity was assessed, once again with the paw edema model, using Wister albino rats [248]. The edema volume was reduced by 85.5% by a dose of 200 mg/kg b.w after 3 h of the MeOH extract, while acute toxicity signs were absent until 5000 mg/kg b.w. The lowest, but still significant effect, was obtained in another study [248] with the aqueous extract of the same taxa: edema volume was reduced after 3 h from 11 to 44% at variable doses from 250 to 1000 mg/kg b.w.

The EtOAc extract of the aerial part of *B. lanata* from China [144] was investigated for its potential anti-inflammatory activity in 2 animal models: the paw edema induced by carrageenan and egg albumin in rats. The effect of edema reduction after treatment with 100 to 400 mg/kg b.w. of extract was dose-dependent: at the highest dose, there was an effect statistically comparable with the positive reference luteolin (**85**). Another study reported the isolation of apigenin-7-*O*-*β*-D-(6′′-*E*-*p*-coumaroyl)glucopyranoside (**139**), apigenin-7-*O*-*β*-D-(2″,6″-*E*-dicoumaroyl)glucopyranoside (**140**), and verbascoside (**227**) from the ethanolic extract of *B. lanata* (China) [168]. Their anti-inflammatory activity was investigated in the same animal models employed for the plant extract. Compound **227** had a higher anti-inflammatory potential than diclofenac (5 mg/kg b.w.), while the activity of compounds **139** and **140** were similar at 20–50 mg/kg b.w. doses. The butanol extract of this species furnished 2 other potentially anti-inflammatory compounds: the flavone C-glycosides panzeroside A (**156**) and B (**157**) [173]. A paw edema reduction volume in rats equal to that of 5 mg/kg b.w. of diclofenac was achieved with 30 mg/kg b.w. of both compounds.

Antibacterial activity

Because of the growing human health danger represented by the antibiotics-resistant bacterial strains and in consideration of the therapeutic uses of many species of *Ballota* and *Otostegia* genera in microbial related pathologies, as well as in wounds and burns treatments, the antimicrobial activity of EOs, plant parts extracts, and also individual compounds has been extensively investigated.

▶ **Table 14** reports a synopsis of the most relevant evidence in the literature.

The MIC and MBC values may vary over a wide interval and are often lower in order of magnitude than that of the antibiotics selected as positive controls. For example, the ethanolic extract of *B. acetabulosa* was found to be significantly active against *Escherichia coli* with MIC and MBC values equal to ampicillin (32, and 64 µg/mL, respectively). On the contrary, the same extract was inactive against *Pseudomonas aeruginosa* (Schroeter) Migula (MIC and MBC 1.02 mg/mL) [250].

The direct relation between the chemical composition of the plant extracts and the antimicrobial activity is not always clearly explainable. Sometimes this relation is evident as in the case of the antimicrobial activity of *B. pseudodictamnus* EO from Greece [220]. Its antibiotic activity was assessed against a panel of 6 pathogenic microorganisms, along with the activity of the principal components of the oil individuated by GC-MS. Unsurprisingly, the MIC of the main component caryophillene oxide (from 0.07 to 5.20 µg/mL) was from 4 to 6 times stronger than that of the whole oil, in which caryophillene oxide is present at 22.8%! The author stated, "The antibacterial property of the oil is suspected to be associated with the high percentage of caryophyllene oxide which is known to possess strong antibacterial activity." The data reported seem to show any other component of this EO as a mere diluent! This is just an example of how the rather vague postulate of the "synergistic effect" of natural product mixtures in biological systems should at least be deeply questioned. Another example of antibacterial activity of a caryophillene rich EO is in the study of *B. saxatilis* subsp. *brachyodonta* from Turkey [221]. A MIC of 50 µg/mL against all of the bacterial genera evaluated was found; caryophillene, caryophillene oxide, and *epi*-bicyclosesquiphellandrene were the main components of the oil.

An example of the lack of a molecular explanation is the study of the activity of the water and methanolic extract of leaves of *B. africana* from South Africa [251]: MICs were reported at 438 and 370 µg/mL versus *Klebsiella pneumoniae* (Schroeter) Trevisan for methanolic and water extracts, respectively. However, an attempt to isolate single bioactive compounds using bio-guided fractionation of the crude extract failed. Additionally, the authors underlined, for not so evident reasons, the apparent discrepancy between the observed antibacterial activity and the lack of

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▶ **Table 6** Distribution of flavones in *Ballota* and *Otostegia* taxa.

No	Name	Taxa
76	apigenin	*B. acetabulosa* [75, 134, 135]; *B. deserti* [89]; *B. hirsuta* [136, 137]; *B. lanata* [138]; *B. nigra* [139]; *B. pilosa* [140]
77	6-methylapigenin	*O. persica* [141, 142]
78	genkwanin	*B. hirsuta* [136]
79	apigenin 7,4′-dimethyl ether	*B. inaequidens* [73, 75, 76]; *B. lanata* [143–145]; *B. pseudodictamnus* [79]; *B. rotundifolia* [73]
80	ladanein	*B. acetabulosa* [73]; *B. hirsuta* [136]; *B. inaequidens* [75]; *B. latibracteolata* [73]; *B. nigra* [115]; *B. rotundifolia* [73]; *B. saxatilis* [73]; *B. saxatilis* ssp. *brachyodonta* [146]
81	salvigenin	*B. glandulosissima* [75, 147]; *B. hirsuta* [136]
82	scutellarein 7,4′-dimethyl ether	*B. acetabulosa* [75, 134]
83	cirsimaritin	*B. andreuzziana* [148]; *B. pilosa* [140]
84	pectolinarigenin	*O. fruticosa* [149]
85	luteolin	*B. acetabulosa* [135]; *B. hirsuta* [136]; *B. lanata* [138]; *B. nigra* [139]
86	luteolin 7-methyl ether	*B. andreuzziana* [148]
87	pilloin	*B. cinerea* [87]
88	luteolin-7,3′,4′-trimethyl ether	*B. glandulosissima* [73, 75, 147]; *B. inaequidens* [73, 75, 76]; *B. lanata* [145]
89	nuchensin	*B. hirsuta* [136]
90	velutin	*B. glandulosissima* [73, 75, 147]; *B. undulata* [150]
91	chrysoeriol	*B. lanata* [138]; *B. nigra* [139]; *O. persica* [141, 142]
92	5-hydroxy-3′,4′,6,7-tetramethoxy flavone	*O. limbata* [151]
93	eupatorin	*O. limbata* [151, 152]
94	3′,6-dihydroxy-4′,5,7-trimethoxy-flavone	*O. persica* [153]
95	4′,5,6,7-tetramethoxyflavone	*B. cinerea* [154]
96	tangeretin	*B. nigra* [155]
97	corymbosin	*B. glandulosissima* [73, 75, 147]
98	6,5′-dihydroxy diosmetin	*O. fruticosa* [156]

▶ **Table 7** Distribution of flavonols in *Ballota* and *Otostegia* taxa.

No	Name	Taxa
99	kaempferol	*B. deserti* [157]; *B. lanata* [29, 138, 145]; *O. persica* [158]
100	quercetin	*B. deserti* [157]; *B. lanata* [29, 138, 143]; *B. macrodonta* [159]; *O. persica* [158, 160]
101	isorhamnetin	*B. lanata* [138, 145]
102	quercetin 3,7,3′,4′-tetramethyl ether	*B. undulata* [150]
103	5-hydroxy-3,7,4′-trimethoxyflavone	*B. inaequidens* [73, 76]; *B. nigra* ssp. *foetida* [73]; *B. rotundifolia* [73]; *B. saxatilis* [73, 75]
104	isokaempferide	*B. hirsuta* [136]
105	kaempferol 3,7,4′-trimethyl ether	*B. saxatils* ssp. *brachyodonta* [146]; *B. undulata* [150]
106	kumatakenin	*B. glandulosissima* [73, 75, 147]; *B. hirsuta* [136]; *B. nigra* ssp. *anatolica* [73]; *B. nigra* ssp. foetida [73]
107	pachypodol	*B. glandulosissima* [73, 75, 147]; *B. inaequidens* [73, 75, 147]; *B. undulata* [150]
108	retusin	*B. glandulosissima* [147]; *B. inaequidens* [75, 76]; *B. nigra* ssp. *foetida* [73]; *B. saxatilis* [73]; *B. saxatils* ssp. *brachyodonta* [146]
109	5-hydroxy-3,6,7,4′-tetramethoxy flavone	*B. inaequidens* [73, 76]; *B. saxatilis* [73]
110	morin	*O. persica* [153, 160]
111	filindulatin	*B. inaequidens* [75]

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▶ **Table 8** Distribution of flavonoid glycosides, flavanones, and flavanols in *Ballota* and *Otostegia* taxa.

No	Name	Taxa
	Flavone glycosides	
112	apigenin-7-*O*-*β*-D-glucopyranoside	*B. acetabulosa* [161]; *B. deserti* [89, 157]; *B. hirsuta* [136, 137]; *B. lanata* [138, 144]; *B. larendana* [162]; *B. nigra* ssp. *foetida* [163]; *B. pseudodictamnus* [162]; *B. undulata* [164]; *O. persica* [141, 142]
113	apigenin-7-*O*-*β*-D-glucuronide	*B. deserti* [89]
114	apigenin-7-*O*-*β*- neohesperidoside	*B. deserti* [89, 90]
115	acacetin-7-*O*-*β*-D-glucopyranoside	*B. acetabulosa* [75, 134]
116	luteolin-7-*O*-*β*-D-glucopyranoside	*B. andreuzziana* [148]; *B. hirsuta* [136, 137]; *B. lanata* [29, 138]; *B. larendana* [162]; *B. macrodonta* [159]; *B. undulata* [150, 164]
117	luteolin-7-*O*-*β*-D-glucuronide	*O. fruticosa* [156]
118	luteolin-7-*O*-*β*-D-rutinoside	*B. hirsuta* [136]
119	diosmetin-7-*O*-*β*-D-glucopyranoside	*B. undulata* [150]
120	chrysoeriol-7-*O*-*β*-D-glucopyranoside	*B. acetabulosa* [75, 134, 161]; *B. hirsuta* [137]; *B. pseudodictamnus* [162]; *O. fruticosa* [149]
121	6,4′-di-O-methyl-scutellarein-7-*O*-*β*-glucopyranoside	*B. andreuzziana* [148]
	Flavonol glycosides	
122	quercetin-3-*O*-*β*-D-glucopyranoside (isoquercetin)	*B. cinerea* [88]; *B. hirsuta* [136]; *B. lanata* [138]
123	quercetin-3-*O*-*β*-galactopyranoside	*B. lanata* [144]
124	rutin	*B. acetabulosa* [135]; *B. cinerea* [88]; *B. deserti* [157]; *B. lanata* [29, 138, 143]; *B. macrodonta* [159]; *B. undulata* [164]
125	quercetin-3-*O*-*α*-L-rhamnopyranoside	*B. lanata* [29, 138]
126	quercetin-3-*O*-*β*-L-rhamnopyranoside	*B. cinerea* [165]
127	quercetin-7-*O*-*β*-L-rutinoside	*B. andreuzziana* [148]
128	isorhamnetin-3-*O*-*β*-D-glucopyranoside	*B. lanata* [138, 144, 145]; *O. persica* [166]
129	isorhamnetin-3-*O*-*β*-D-rutinoside	*B. lanata* [138, 144]
130	isorhamnetin-3-*O*-*β*-D-galactopyranoside	*B. lanata* [138]
131	isorhamnetin-7-*O*-*β*-D- rutinoside	*B. lanata* [145]
132	kaempferol-3-*O*-*β*-D-glucopyranoside	*B. lanata* [138, 143, 145]
133	kaempferol-3-*O*-*β*-D-rutinoside (nicotiflorin)	*B. cinerea* [88]; *B. lanata* [138]
134	kaempferol-7-*O*-*β*-D-glucopyranoside	*B. lanata* [138]
135	kaempferol-3-*O*-[*β*-D-glucopyranosyl-(1 → 2)-{*β*-D-glucopyranosyl-(1 → 3)}-{*β*-D-glucopyranosyl-(1 → 4)}-*α*-L-rhamnopyranoside]-7-O-[*α*-L-rhamnopyranoside]	*O. limbata* [167]
	Acyl flavonoid glycosides	
136	apigenin-7-(*p*-coumaroyl)-glucoside	*B. hirsuta* [136, 137]
137	apigenin-7-*O*-*β*-D-(3′′-*p*-*E*-coumaroyl)glucopyranoside	*B. larendana* [162]
138	apigenin-7-*O*-*β*-D-(4′′-*E*-*p*-coumaroyl)glucopyranoside (echinaticin)	*B. acetabulosa* [161]; *O. persica* [141, 142]
139	apigenin-7-*O*-*β*-D-(6′′-*E*-*p*-coumaroyl)glucopyranoside (terniflorin)	*B. deserti* [89]; *B. lanata* [138, 168, 169]; *B. larendana* [162]; *B. pilosa* [140]
140	apigenin-7-*O*-*β*-D-(2″,6″-*E*-dicoumaroyl)glucopyranoside	*B. lanata* [168]
141	luteolin-7-(*p*-coumaroyl)glucopyranoside	*B. hirsuta* [137]
142	luteolin-7-lactate	*B. nigra* [170]
143	luteolin-7-*O*-[2-*O*-*β*-D-glucopiranosyl-lactate]	*B. nigra* [170]
144	chrysoeriol-7-(*p*-coumaroyl)glucopyranoside	*B. hirsuta* [137]
145	chrysoeriol-7-*O*-*β*-D-(3′′-*E*-*p*-coumaroyl)-glucopyranoside	*B. acetabulosa* [161]; *B. pseudodictamnus* [162]
146	chrysoeriol-7-*O*-*β*-D-(3′′-*Z*-*p*-coumaroyl)glucopyranoside	*B. acetabulosa* [161]
147	chrysoeriol-7-*O*-*β*-D-(6′′-*p*-coumaroyl)glucopyranoside	*B. lanata* [138]; *B. undulata* [150]
148	kaempferol-7-*O*-*β*-D-(6′′-*p*-coumaroyl)glucopyranoside	*B. lanata* [138]
149	kaempferol-3-*O*-*β*-D-(6′′-*p*-coumaroyl)glucopyranoside	*B. lanata* [138]

continued

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▶ **Table 8** *Continued*

No	Name	Taxa
150	5,6,7,4′-tetrahydroxyflavone-7-*O*-*β*-D-(6′′-*E*-*p*-coumaroyl)glucopyranoside	*B. lanata* [144]
151	5,6,7,4′-tetrahydroxyflavone-7-*O*-*β*-D-(6′′-*E*-caffeoyl)glucopyranoside	*B. lanata* [144]
152	leufolins B	*B. arabica* [171]
153	5-hydroxy-2-(4-hydroxyphenyl)-4-oxo-7-[(*α*-L-rhamnopyranosyl)oxy]-4H-chromen-3-yl *β*-D-glucopyranosyl-(1 → 2)-[*β*-D-glucopyranosyl-(1 → 4)]-[6-O-[(2*E*)-3-(4-hydroxyphenyl) prop-2-enoyl]-*β*-D-glucopyranosyl-(1 → 3)]-*α*-L-rhamnopyranoside	*O. limbata* [172]
154	5-hydroxy-2-(4-hydroxyphenyl)-4-oxo-7-[(*α*-L-rhamnopyranosyl)oxy]-4H-chromen-3-yl [6-O-[(2*E*)-3-(4-hydroxyphenyl)prop-2-enoyl]-*β*-D-glucopyranosyl-(1 → 2)]-[*β*-D-glucopyranosyl-(1 → 4)]-[6-O-[(2*E*)-3-(4-hydroxyphenyl)prop-2-enoyl]- *β*-D-glucopyranosyl-(1 → 3)]-*α*-L-rhamnopyranoside	*O. limbata* [172]
155	kaempferol-3-*O*-[*β*-D-glucopyranosyl-(1 → 4)-*β*-D-6′′′′′[4-hydroxy-(*E*)-cinnamoyl]glucopyranosyl-(1 → 3)-[*β*-D-glucopyranosyl-(1 → 2)]-*α*-L-rhamnopyranoside]-7-*O*-[*α*-L-rhamnopyranoside]	*O. limbata* [167]
	C-glycosyl flavonoids	
156	panzeroside A	*B. lanata* [173]
157	panzeroside B	*B. lanata* [173]
158	isovitexin	*O. persica* [158]
159	vicenin-2	*B. aucheri* [174]; *B. hirsuta* [136]; *B. nigra* ssp. *foetida* [163]; *O. fruticosa* [156]; *O. persica* [166]
	Flavanones, flavanone glycosides	
160	naringenin	*B. acetabulosa* [135]
161	naringenin-7-*O*-*β*-D-glucopyranoside	*B. macrodonta* [159]
162	naringin	*B. acetabulosa* [135]
163	leufolins A	*B. arabica* [171]
	Flavanols	
164	epicatechin	*B. acetabulosa* [135]; *B. macrodonta* [159]
165	catechin	*B. macrodonta* [159]
166	epigallocatechin gallate	*B. macrodonta* [159]

resveratrol in the extract. Furthermore, in one case, the demonstration of the lack of antibacterial activity versus *Propionicbacterium acnes* (Gilchrist) Douglas of Italian *B. nigra* extract demonstrated the inconsistency of its claimed ethnopharmacological use as an anti-acne remedy [262]. In some cases, the antimicrobial activity of a certain species may vary greatly depending on the extraction solvent and the target investigated. A clear example is the case of the aerial part of Iranian *O. persica* [261]: the initial ethanolic extract was portioned in fractions soluble in *n*-Hex, $CHCl_3$, and finally MeOH. The lowest MIC and MBC values were 1.25 mg/mL for the $CHCl_3$ ext. against *Staphylococcus aureus* and *Enterococcus faecalis*, while the MeOH extc. had a 25 mg/mL MIC for *Listeria monocytogens* (E. Murray et al.) Pirie. Finally, the bacteria species *E. coli, P. aeruginosa, Salmonella* spp., *Klebsiella* spp., and *Proteus* spp. were completely insensitive to all of the extracts.

In other cases, the different geographical origin of the plant material may be the cause of strong differences in the bioactivity, as is the case of the EO derived from *O. fruticosa*. The plant harvested in Egypt is characterized by antibacterial activity with MIC in the order of µg/mL [224]. On the contrary, the same taxa from Yemen show MIC values 2 order of magnitude higher than the former [222]. This difference can be explained by the deep difference in the composition of the 2 oils, regarding their main components in particular, as discussed above.

▶ **Table 14** includes cases where the crude extracts were further portioned with organic solvents in the attempt to concentrate the more active compounds [253, 254, 257], as well as other cases, where the bioactivity was evaluated for single isolated molecules [76, 89, 187]. In most, highly polar extracts obtained with protic solvents and water contained mainly phenols, phenylpropanoids, and glycosylates. Only 1 case reports the isolation and the measurement of the antibacterial activity of terpenes from the Ac extract of *B. saxatilis* subsp. *saxatilis* from Turkey [80].

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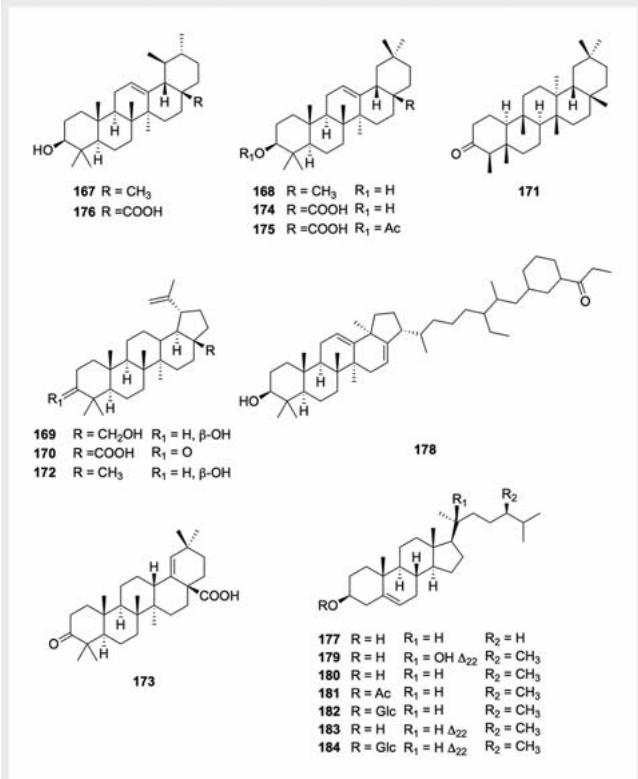
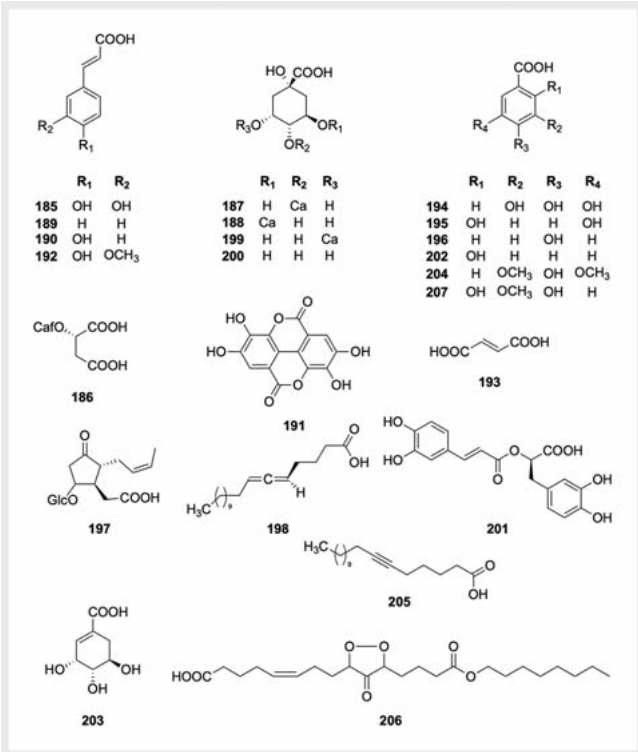
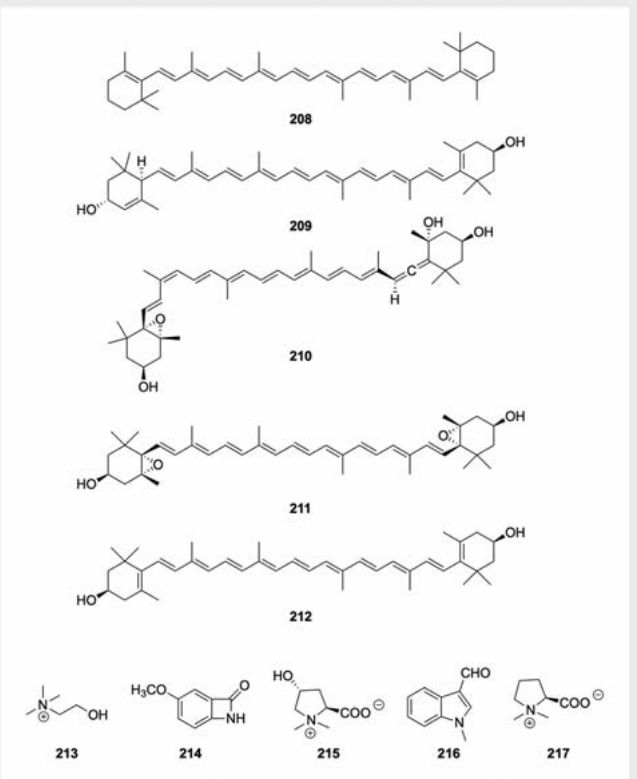


▶ **Fig. 11** Structures of triterpenes and steroids.



▶ **Fig. 12** Structures of carboxylic acids.



▶ **Fig. 13** Structures of carotenoids and nitrogen containing compounds.

Antifungal activity

The general points discussed for antibacterial activity are valid also in this case, as methodological approaches are obviously similar and a lot of investigations involve both bacterial and fungal species as targets. ▶ **Table 15** summarizes the most relevant data reviewed.

Antitumor activity

The EO of *Ballota undulate, B. saxatilis*, and *B. nigra* collected in Italy were assessed for their *in vitro* cytotoxicity toward the Hep-G2 hepatocarcinoma and MCF-7 breast carcinoma cell lines [218]. The 3 oils showed moderate inhibition values against the former target (IC_{50}: 54.7, 65.4, and 69.9 µg/mL, respectively) and low values for latter (> 100 µM). Sesquiterpenes were found as major components in the oils. The MCF-7 cells were instead more sensitive to the EO of *O. fruticosa* with an IC_{50} of 55.1 µg/mL. This taxon was moderately active also against MDA-MB-231 cells with IC_{50} of 72.3 µg/mL [222].

Rhabdomyosarcoma cells were found to be sensitive to treatment with the methanolic extract of *O. limbata* from Pakistan [266]. Cell viability tests showed up to 93 % mortality after 72 h, a higher level than cisplatin (23 %).

The EtOH extract of AP of *B. cinerea* was assessed for its cytotoxicity against several cancer cell lines, showing moderate activity [267] with the following LC_{50} values (µg/mL): 131.8 for SK-MEL 2, 275.4 for BE (2) C, and 302.0 for U87MG.

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▶ **Table 9** Distribution of triterpenes, steroids, carboxylic acids, and carotenoids in *Ballota* and *Otostegia* taxa.

No	Names	Taxa
	Triterpenoids	
167	α-amyrin	*O. fruticosa* [175]
168	β-amyrin	*B. cinerea* [154, 176], *O. persica* [177]
169	betulin	*B. cinerea* [176],
170	betulonic acid	*B. cinerea* [154]
171	friedelin	*B. aucheri* [174], *B. cinerea* [154]
172	lupeol	*O. fruticosa* [175]
173	moronic acid	*B. cinerea* [178]
174	oleaonolic acid	*B. nigra* [179], *B. cinerea* [180] *O. fruticosa* [156]
175	oleanolic acid 3-acetate	*B. pilosa* [140]
176	ursolic acid	*B. arabica* [181], *B. nigra* [179], *O. fruticosa* [156]
	Steroids	
177	campesterol	*O. persica* [177]
178	3β-hydroxy-35-(cyclohexyl-5′-propan-7′-one)-33-ethyl-34-methyl-bacteriohop-16-ene	*B. cinerea* [182]
179	leucisterol	*B. arabica* [181]
180	β-sitosterol	*B. arabica* [181], *B. cinerea* [87, 154, 176], *B. deserti* [24], *B. lanata* [29, 143], *B. nigra* [115, 183], *B. pilosa* [140], *O. fruticosa* [156, 175], *O. persica* [177]
181	β-sitosterol 3-acetate	*O. persica* [177]
182	β-sitosterol-3-*O*-β-D-glucopiranoside	*B. cinerea* [154], *B. deserti* [24], *B. lanata* [29, 143], *B. pilosa* [140]
183	stigmasterol	*B. aucheri* [174], *B. cinerea* [87, 176, 182], *B. deserti* [24], *B. lanata* [143], *B. pilosa* [140], *B. undulata* [81], *O. integrifolia* [100], *O. persica* [177]
184	stigmasterol-3-*O*-β-D-glucopiranoside	*B. pilosa* [140]
	Carboxylic acids	
185	caffeic acid	*B. acetabulosa* [135], *B. arabica* [184], *B. lanata* [29, 145], *B. macrodonta* [159], *B. nigra* [139, 185], *O. fruticosa* [156], *O. persica* [177]
186	*E*-caffeoyl-L-malic acid	*B. hirsuta* [186], *B. lanata* [29], *B. nigra* [185–189], *B. pseudodictamnus* [162], *B. rupestris* [186]
187	4-*O*-caffeoylquinic acid	*B. macrodonta* [159]
188	chlorogenic acid	*B. acetabulosa* [135], *B. lanata* [29], *B. macrodonta* [159], *B. nigra* [139, 185]
189	*E*-cinnamic acid	*B. deserti* [157], *O. persica* [158]
190	*E*-coumaric acid	*B. acetabulosa* [135], *B. hirsuta* [137], *B. macrodonta* [159]
191	ellagic acid	*B. macrodonta* [159]
192	ferulic acid	*B. arabica* [184], *B. macrodonta* [159], *B. nigra* [139], *O. fruticosa* [149]
193	fumaric acid	*B. nigra* [185]
194	gallic acid	*B. acetabulosa* [135], *B. arabica* [184], *B. cinerea* [176], *B. deserti* [157], *B. macrodonta* [159]
195	gentisic acid	*B. macrodonta* [159]
196	4-hydroxy benzoic acid	*B. arabica* [181], *B. deserti* [157], *B. macrodonta* [159], *O. persica* [177]
197	jasmonic acid 5′-β-D-glucopyranosyloxy	*B. cinerea* [88]
198	laballenic acid	*B. nigra* [188]
199	neochlorogenic acid	*B. lanata* [29], *B. macrodonta* [159]
200	quinic acid	*B. nigra* [185]
201	rosmarinic acid	*B. acetabulosa* [135], *B. macrodonta* [159]
202	salicylic acid	*B. macrodonta* [159]
203	shikimic acid	*B. nigra* [185]
204	syringic acid	*B. macrodonta* [159]
205	tariric acid	*B. cristata* [190]
206	urticic acid	*B. arabica* [181]
207	vanillic acid	*B. macrodonta* [159]

continued

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▶ **Table 9** *Continued*

No	Names	Taxa
	Carotenoids	
208	carotene	*B. lanata* [29]
209	lutein	*B. lanata* [29]
210	neoxanthin	*B. lanata* [29]
211	violaxanthin	*B. lanata* [29]
212	zeaxanthin	*B. lanata* [29]

Precalyone (**45**) was isolated, together with other diterpenes, from the ethanolic extract of the leaves and the stems of *B. cinerea* [86]. This compound was active against the murine P-388 lymphocytic leukemia.

Docking studies of 18 phyto compounds from the plant *B. nigra* of the family Lamiaceae were carried out. From the results, ballotinone (**10**), and ballonigrin (**5**) were found to have the best binding efficiency with the active site residues of the protein. The binding energies of the 2 compounds were − 12.0691 kcal/mol and − 10.2564 kcal/mol, respectively. This study provides a promising anti-cervical cancer inhibitor for further drug development [268].

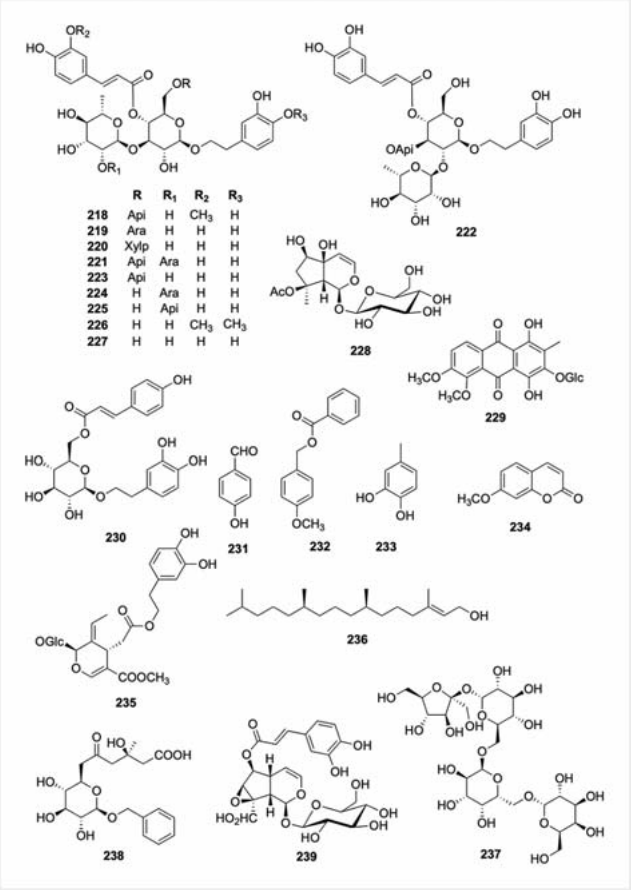
7*α*-Acetoxyroyleanone (**73**), also occurring in *B. nigra* [115], was shown to be an active anticancer agent against both MIAPaCa-2 and melanoma (MV-3) cancer cell lines (IC_{50} = 4.7 and 7.4 µg/mL, respectively) [269]. Additionally, it also exhibited cytotoxic activity against 5 more human cancer cell lines including, breast (MCF-7), human leukemia (CEM and HL-60), murine skin (B16), and colon cancer (HCT-8) cell lines in the range of IC_{50} = 0.9–7.6 µg/mL. Its cytotoxic activity seemed to be related to inhibition of DNA synthesis [270].

The anticancer activity of marrubenol (**36**), present in *B. pseudodictamnus* [79], against osteosarcoma cells along with evaluating its effects on autophagic cell death, reactive oxygen species generation and cell migration and invasion tendency was evaluated. The results indicated that compound **36** exhibited an IC_{50} value of 45 µM and exerted its cytotoxic effects in a dose-dependent manner. Moreover, it was observed that the drug inhibited colony formation and induced autophagy dose-dependent [271].

A moderate antiproliferative effect on lung adenocarcinoma cell line (H1975 and XLA-07) and mouse mononuclear macrophage leukemia cell line (RAW264.7) was detected for leoheterin (**34**) [272], a labdane diterpenoid occurring in *B. aucheri* [71, 74, 97] and *O. fruticosa* [82, 98].

Other bioactivities *in vitro*

The efficacy of *B. nigra* in its traditional neurosedative use was proven by assessing the binding activity in dopaminergic, benzodiazepine, and morphinic receptors of a number of compounds isolated from the leaf extract in EtOH/H_2O 1 : 1 [236]: (+)-(*E*)-caffeoyl-L-malic acid (**186**), verbascoside (**227**), forsythoside B (**223**), arenarioside (**220**), and ballotetroside (**221**). These molecules were active with IC_{50} values ranging from 0.4 to 10 µM.



▶ **Fig. 14** Structures of other compounds.

The labdane diterpene cinereanoid D (**16**), the flavonoid glycosides isoquercetin (**122**), nicotiflorin (**133**), and martynoside (**226**) isolated from the aerial part extract (95% EtOH) of *B. cinerea,* collected in India [88], significantly inhibited the ATP binding of a tumor growth-promoting heat shock protein, Hsp90. No significant binding inhibition was revealed for the protein Hsp70.

B. nigra [253] and *B. pseudodictamnus* [257] from Pakistan were evaluated by the same group for their anti-leishmanial activity. The extracts of the plant stems, leaves, and roots in EtOH were partitioned between water and several organic solvents: *n*-Hex, EtOAc, chloroform, and *n*-BuOH. The single subfractions of the

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▶ **Table 10** Distribution of *N*-derivatives, phenylpropanoids, and other metabolites in *Ballota* and *Otostegia* taxa.

No	Names	Taxa
	Nitrogen-containing compounds	
213	choline	*B. nigra* subsp. *foetida* [191]
214	cinerealactam E	*B. cinerea* [88, 182]
215	4-hydroxyprolinebetaine	*B. nigra* [188], *B. undulata* [150]
216	1-methylindole-3-carboxaldehyde	*B. cinerea* [87]
217	stachydrine	*B. lanata* [138, 192], *B. nigra* [188], *B. nigra* subsp. *foetida* [191], *B. undulata* [150]
	Penylpropanoids	
218	alyssonoside	*B. nigra* [185, 187]
219	angoroside A	*B. nigra* [187]
220	arenarioside	*B. nigra* [94, 187, 193]
221	ballotetroside	*B. nigra* [94, 185, 187, 194]
222	betonyoside F	*B. undulata* [150]
223	forsythoside B	*B. deserti* [89, 90], *B. hirsuta* [186], *B. nigra* [94, 115, 185–189, 193], *B. pseudodictamnus* [162], *B. rupestris* [186], *B. undulata* [150]
224	lavandulifolioside	*B. nigra* [187]
225	lysionotoside	*B. undulata* [150]
226	martynoside	*B. cinerea* [88], *B. nigra* [115]
227	verbascoside (acteoside)	*B. deserti* [89, 90], *B. hirsuta* [186], *B. lanata* [29, 144, 168], *B. nigra* [94, 185–189, 193, 195], *B. pseudodictamnus* [162], *B. rupestris* [186], *B. undulata* [150]
	Other metabolites	
228	8-*O*-acetylharpagide	*O. fruticosa* [82]
229	anthroquinone1,4-dihydroxy-6,7-dimethoxy 2-methyl 3-O-*β*-D-glucopyranoside	*B. cinerea* [165]
230	eutigoside A	*B. acetabulosa* [161]
231	4-hydroxybenzaldehyde	*B. macrodonta* [159]
232	4-methoxybenzyl benzoate	*B. arabica* [184]
233	4-methyl-catechol	*B. deserti* [157]
234	7-methoxy coumarin	*B. lanata* [145]
235	oleuropein	*B. acetabulosa* [135]
236	phytol	*B. deserti* [24], *B. nigra* [183], *B. nigra* subsp. *anatolica* [196]
237	stachyose	*B. nigra* subsp. *foetida* [197]
238	undatuside A	*B. cinerea* [88]
239	verminoside	*B. undulata* [150]

2 species showed the ability to inhibit the parasite development process at various stages.

The leaves of *B. deserti* harvested in Tunisia were extracted in a solvent of increasing polarity [25]. MeOH, BuOH, and EtOAc extracts showed significant antiviral activity against coxsakie B3 virus with IC_{50} values ranging from 100 to 135 µg/mL and with a selective index above 3.

The genotoxic and antigenotoxic activities of some *B. deserti* AP extracts in various solvents were evaluated on *E. coli* PQ37 cells by the SOS Chromotest. Additionally, a number of pure compounds isolated from the same plant were included in this investigation [89]. EtOAc, MeOH, and BuOH extracts proved moderately to highly genotoxic in a dose-dependent manner, while apigenin-7-*O*-*β*-neohesperidoside (**114**), verbascoside (**227**), apigenin-7-*O*-*β*-D-glucopyranoside (**112**), and apigenin (**76**) resulted as marginally genotoxic. Furthermore, the protective effect of all extracts and the isolated compounds was studied on nitrofurantoin (NF) induced damage. MeOH, EtOAc, and BuOH extracts significantly decreased the induction factor of NF by 89.8%, 94.3%, and 96.2%, respectively, while compounds **76, 112–114, 139, 223, and 227** decreased the genotoxicity by a factor of 65 to 97%.

Insecticidal activity

The hot water extract of the leaves of *B. undulata* from Jordan [273] was effective as a repellent agent against the sweet potato parasite *Bemisia tabaci* (Gennadius). A set of tomato leaves treated with the extract was compared with untreated tomato leaves, demonstrating a significant difference (analysis of variance test) in the number of insects that attacked each group. The same taxon, in the form of leaves brewed in hot water, showed acaricidal

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▶ **Table 11** Occurrence of non-volatile metabolites in taxa of *Ballota* and *Otostegia*.

Taxa	Diterpenes	Flavonoids	Others
B. acetabulosa	**5, 18, 25, 33**	**76, 80, 82, 85, 112, 115, 120, 124, 138, 145, 146, 160, 162, 164**	**185, 188, 190, 194, 201, 230, 235**
B. africana	**25**		
B. andreuzziana	**25**	**83, 86, 116, 121, 127**	
B. antalyensis	**5, 18**		
B. arabica	**75**	**152, 163**	**176, 179, 180, 182, 185, 192, 194, 196, 206, 232**
B. aucheri	**4, 5, 10, 27, 28, 29, 30, 31, 34, 44, 46**	**159**	**185, 188, 190, 194, 201, 230, 235**
B. cinerea	**12, 13, 14, 15, 16, 45, 74**	**87, 95, 122, 124, 126, 133**	**168–171, 173, 174, 178, 180, 182, 183, 194, 197, 214, 216, 226, 229, 238**; cetyl alcohol, glucose, fructose, arabinose, palmitic acid, stearic acid, oleic acid, oxalic acid, tartaric acid [176]; hentriacontane, triacontane [116]; pentacosane, octacosanol [154]
B. cristata	**5, 18, 25**		**204**; linoleic acid, oleic acid, palmitic acid, stearic acid, linolenic acid [190]
B. deserti	**2, 3, 19, 17, 20, 21, 24, 37–40**	**76, 99, 100, 112–114, 124, 139**	**180, 182, 183, 189, 194, 196, 223, 227, 233, 236**
B. glandulosissima		**81, 88, 90, 97, 106, 107, 108**	
B. hirsuta	**25**	**76, 78, 80, 81, 85, 89, 104, 106, 112, 116, 118, 120, 122, 136, 141, 144, 159**	**186, 190, 223, 227**
B. hispanica	**51, 52**		
B. inaequidens	**5, 25**	**79, 80, 88, 103, 107–109, 111**	
B. lanata	**5, 32**	**76, 79, 85, 88, 91, 99, 100, 101, 112, 116, 122–125, 128–132, 134, 139, 140, 147–151, 156, 157**	**176, 180, 182, 183, 185, 186, 188, 199, 208–212, 217, 227, 234**
B. larendana	**5, 18**	**112, 116, 137, 139**	
B. latibracteolata	**18**	**80**	
B macrodonta	**18**	**100, 116, 124, 161, 164–166**	**185, 187, 188, 190–192, 194–196, 199, 201, 202, 204, 207, 231**
B. nigra	**1, 5, 32,73**	**76, 80, 85, 91, 96, 142, 143**	**174, 176, 180, 182, 185, 186, 188, 192, 193, 198, 200, 203, 215, 217–221, 223, 224, 226, 227, 236**; oxalic acid, aconitic acid, citric acid, ascorbic acid, malic acid [185]; linoleic acid α-linolenic acid, oleic acid, palmitic acid, stearic acid [198]
B. nigra subsp. *anatolica*		**106**	**236**; 10-undecenoic acid, myristic acid, palmitoleic acid, palmitic acid, 11,13-dimethyl-12-tetradecen-1-ol acetate, linoleic acid, oleic acid, linolenic acid, stearic acid, arachidic acid, 7-methyl-6-hexadecenoic acid, behenic acid [196]
B. nigra subsp. *foetida*	**5, 9, 10, 37, 47**	**103, 106, 108, 112, 159**	**213, 217, 237**; palmitic acid, stearic acid, octadecenoic acid, octadecadienoic acid, octadecatrienoic acid [199]
B. nigra f. uncinata.	**18**		
B. pilosa		**76, 139**	**175, 180, 182–184**
B. pseudodictamnus	**5, 33, 36**	**79, 112, 120, 145**	**186, 223, 227**
B. pseudodictamnus subsp. *lycia*	**18, 25**		
B. rotundifolia	**18, 25**	**79, 80, 103**	
B. rupestris	**5, 8, 49**		**186, 223, 227**
B. saxatilis	**5, 18, 25, 33**	**80, 103, 108, 109**	
B. saxatilis subsp. *brachyodonta*	**5, 18**	**80, 105, 108**	

continued

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▶ **Table 11** *Continued*

Taxa	Diterpenes	Flavonoids	Others
B. undulata	**5, 8, 10, 26**	**90, 102, 105, 107, 112, 116, 119, 124, 147**	**183, 215, 217, 222, 223, 225, 227, 239**; (−)-carvone, [81]
O. fruticosa	**5, 22, 23, 34, 35, 41, 42, 46, 50**	**84, 98, 117, 120, 159**	**167, 174, 176, 180, 185, 192**; octacosane, palmitic acid, linoleic acid, arachidic acid [175]
O. integrifolia	**43, 48**		**183**; pentatriacontane [100]
O. limbata	**6, 7, 53–72**	**92, 93, 135, 153–155**	
O. persica	**56, 59, 71, 72**	**77, 91, 94, 99, 100, 110, 112, 128, 158, 159**	**168, 177, 180, 181, 183, 185, 189, 196**; gerianol, eugenol, ceryl alcohol, hentiacontane [177]

activity against the spider mite *Tetranychus urticae*. A high mortality (53%) was achieved by treating adults with the extract, while the eggs remained unaffected [274].

An insect repellent activity was also disclosed for *O. integrifolia* from Ethiopia [275]. The headspace of fresh leaves, dried leaves, and burned dried leaves were evaluated giving a repellent ratio of 29–56% in an elegant experimental setting developed by the author. This activity was shown to be associated with the presence of *β*-ocimene in the headspace blend.

The *n*-Hex extract of *O. limbata* (Pakistan) showed larvicidal activity against the banana parasite *Drosophila melanogaster* Meigen [276]. The crude solid extract was mixed with overripe banana at 2–6% w/w and larvae were let to feed. A concentration dependent mortality from 12 to 89% was observed. Also, a pupation reduction effect was established with a ratio of development dropping from 88 to 23%, depending on the extract concentration (0.5–2.0%).

The Ac extract of *O. persica* leaves collected in Iran [277] was studied as a pesticide against *Aphis fabae* Scopoli, *Aphis gossypii* Glov., *Myzus persicae* Sulzer, and *Tribolium castaneum* Herbst. The maximum mortalities of individuals after 48 h of treatment at 80 µL/mL dose of extract were 55, 58, 88, and 34%, respectively. The prolongation of exposure time to 60 h did not appear to significantly improve the mortality rate.

An Ac extract of *B. hirsuta* (AP) from Spain [278] caused a significant growth inhibition in the *T. castaneum* larvae (29%) accompanied by 20% mortality. This effect was related to the harvesting time, as the plant taken in November was active, while a sample collected in April was inactive.

Effects on central nervous system

The extract of *B. limbata* (Pakistan) leaves in *n*-buthanol was active as antitussive by reducing the SO_2-induced cough in mice. The treatment of animals with 800 mg/kg b.w. of the extract caused the cough episodes to be reduced from 46 to 12 in 60 min; an efficacy analogous to that of the standard antitussive drugs codeine and dextromethorphan [279]. The toxicity test proved the extract to be inoffensive until the dose of 5000 mg/g b.w.

The brew (in hot water) of the AP of *B. nigra* subsp. *anatolica* from Turkey possess both antidepressant and anxiolytic activities in rats, determined with the forced swimming and the elevated plus-maze tests [280].

Two extracts of *O. persica* harvested in Iran were prepared by suspending the AP of the plant in *n*-Hex and 80% EtOH and were tested for the alleviating effect in the opioid withdrawal syndrome [281], as this is a traditional use in Iran folk medicine. Male mice were intoxicated with morphine and the withdrawal signs (jumping, rearing, diarrhea, piloerection, tremor, and ptosis) were recorded after injection of naloxone in untreated animals, treated with clonidine (0.2 mg/kg b.w.) and with increasing doses of both the extracts (500–1500 mg/kg b.w.). All of the clinical signs were reduced significantly to levels comparable to those obtained with clonidine at the maximum dose of utilized ethanolic extract. The *n*-Hex extract, however, was only able to reduce diarrhea.

An anticonvulsant effect was evidenced in the MeOH extract of *O. persica* [282], sustaining the traditional use of this plant in seizure management with scientific evidence. Convulsions were induced in mice with pentylenetetrazole, followed by an IP injection of 800 mg/kg b.w. which had a 93% protective effect, comparable to that of benzodiazepine.

The extract of AP of *B. glandulosissima* in water were investigated for their antinociceptive activity in mice by acetic acid-induced "writhing" and "tail-flick" tests [283]. A lethal dose of 8.85 g/kg b.w. was determined. The extract, intraperitoneally administrated at 100 and 200 mg/kg b.w. doses, had promising antinociceptive activity, comparable to acetylsalicylic acid, utilized as a positive control.

An analgesic effect similar to paracetamol was obtained with the MeOH extract of *B. deserti* AP from Algeria [248] when administrated at 400 mg/kg b.w. to albino rats. Acetic acid induced abdominal writhes were reduced by 73%.

Metabolism control effects

The extract of *B. nigra* from Jordan, obtained by brewing the AP in EtOH water 7:3, was proven to possess very interesting hypoglycemic activity both in healthy and in allossana-induced diabetic albino rats. After a single dose treatment of 400 mg/g b.w., the first group had a glucose blood concentration reduction from 96 to 62 mg/dL after 6 h, while for the second group, the value dropped from 324 to 271 mg/dL [284]. In another study by the same authors [285], an analogous *B. nigra* preparation administrated at the same dose for 7 d was also effective in reducing hematic cholesterol (from 193 to 144 mg/dL), triglycerides (from 97 to 83 mg/dL), and CK protein (from 431 to 348 IU/L).

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▶ **Table 12** Main compounds (> 3 %) of the essential oils from *Ballota* and *Otostegia* taxa.

Taxa		Origin	Main compounds	Ref.
B. andreuzziana	F	G. Akhdar, Libya	caryophyllene (63.1), cis-γ-bisabolene (26.3), selinene (5.0)	[200]
B. aucheri	AP	Fars, Iran	α-cadinol (21.0), dehydroaromadendrene (11.8), β-caryophyllene (8.1), carvone (6.4), spathulenol (6.0), linalool (4.8), (*Z*)-methyl isoeugenol (4.1), α-santalene (3.5)	[201]
B. deserti	AP	Djelfa, Algeria	germacrene D (45.7), β-bourbonene(4.0), α-terpinolene (3.9), δ-cadinene (3.8), 1-octen-3-ol (3.7), α-copaene (3.5)	[202]
	AP	Ghardaïa, Algeria	9-methyl-undecene (21.3), δ-cadinene (12.2), germacrene D (11.9), *cis*-phytol (7.7), α-cubebene (4.4)	[203]
	AP	Algerian Sahara	tetracosane (31.1), germacrene D (7.9), δ-cadinene (6.5), α-cadinol (6.3) *t*-cadinol (5.8), β-elemene (3.8)	[204]
B. hispanica	AP	Sicily, Italy	α-elemol (10.9), α-ylangene (8.5), γ-dodecalactone (5.1), manoyl oxide (4.8), γ-eudesmol (4.2), β-eudesmol (3.7), 1-pentadecene (3.7), germacrene D (3.5),	[205]
B. lanata	AP	Buryatia, Russia	palmitic acid (14.3), camphor (12.4), α-pinene (10.3), linalool (9.1), β-caryophyllene (8.3), terpinen-4-ol (6.4), phytol (4.8), caryophyllene oxide (4.2), *p*-mentha-3-en-8-ol (3.3)	[29]
	AP	Gobi, Mongolia	camphor (14.4), α-pinene, (11.3), terpinenol-4 (5.3), 6,10,14-trimethyl-2-pentadecanone (4.7), β-caryophyllene (3.5), β-humulene (3.2), α-thujene (3.1)	[206]
B. macedonica	AP	Debar, Macedonia	germacrene D (24.6), (*E*)-caryophyllene (16.5), carotol (13.7), caryophyllene oxide (3.5)	[207]
	AP	Prizren, Serbia	carotol (52.1), germacrene D (8.6), (*Z*)-hex-3-en-1-ol (7.0), (*E*)-caryophyllene (6.5) oct-1-en-3-ol (3.8)	[207]
B. nigra	AP	Mazandaran, Iran	caryophyllene oxide (7.9), *epi*-α-muurolol (6.6), δ-cadinene (6.5), α-cadinol (6.3), γ-amorphene (4.3), β-bourbonene (4.1), 6,10,14-trimethyl-2-pentadecanone (4.0), (*E*)-caryophyllene (4.0), germacrene D (3.8), aromadendrene (3.4), γ-muurolene (3.2), germacrene D-4-ol (3.2), α-bisabolol (3.2), α-amorphene (3.0)	[208]
	S	Jadovnik Mt., Serbia	β-caryophyllene (35.4), germacrene D (27.4), α-humulene (7.4), δ-cadinene (3.8), (*E*)-phytol (2.5)	[209]
	L	Jadovnik Mt., Serbia	β-caryophyllene (39.1), germacrene D (35.7), α-humulene (10.4), (*E*)-phytol (3.8)	[209]
	R	Jadovnik Mt., Serbia	*p*-vinylguiacol (9.2), borneol (7.5), myrtenol (7.1), *trans*-pinocarveol (5.2), 1-octen-3-ol (5.1), pinocarvone (4.4), 2-methyl-3-phenylpropanal (4.3), *p*-cymen-8-ol (4.3), *trans*-carveol (3.5)	[209]
	AP	Golestan, Iran	β-pinene (39.0), α-pinene (34.5), sabinene (7.7), α-phellandrene (4.1)	[210]
	corollas	Kharkov, Ukraine	palmitic acid (573)[a], 2,2,6-trimethyl-4-methylene-2H-pyran (172)[a], hexahydrofarnesylacetone (167)[a], miristic acid (100)[a], caryophyllene oxide (57)[a], pentadecanoic acid (50)[a], palmitoliec acid (40)[a], germacrene D (40)[a] [a]mg/kg	[211]
	calyx	Kharkov, Ukraine	palmitic acid (1620)[a], dodecanal (519)[a], palmitoliec acid (306)[a], miristic acid (271)[a], pentadecanoic acid (182)[a], lauric acid (67)[a], *trans*-isoelemicin (67)[a], hexahydrofarnesylacetone (60)[a], pentadecene (54)[a], methyleugenol (40)[a] [a]mg/kg	[211]
	L	Kharkov, Ukraine	palmitic acid (656)[a], palmitoliec acid (197)[a], miristic acid (187)[a], pentadecanoic acid (121)[a], farnesylacetone (69)[a], dihydroactinidiolide (44)[a] [a]mg/kg	[211]
	S	Kharkov, Ukraine	methylsalicilate (313)[a], palmitic acid (130)[a], 2,2,6-trimethyl-4-methylene-2H-pyran (42)[a], miristic acid (42)[a] [a]mg/kg	[211]
B. nigra L. subsp. *anatolica*	AP	Mazandaran, Iran	germacrene D (18.1), nerolidol epoxyacetate (15.4), sclareol oxide (12.1), linalyl acetate (11.5), β-caryophyllene (10.5), spathulenol (9.0), linalool (5.2), longipinene epoxide (4.7)	[212]
	F	Çamlica, Turkey	hexenal (21.2), (*E*)-β-caryophyllene (10.0), germacrene D (7.8), *cis*-3-hexene-1-ol (6.8), pentanal (6.9), limonene (5.2), (*E*)-2-hexenal (3.0)	[213]
	AP	Muğla, Turkey	hexadecanoic acid (40.9), β-bisabolene (13.4), hexahydrofarnesyl acetone (7.9), 1-isobutyl-4-isopropyl-2,2-diemethyl succinate (6.6), β-eudesmol (3.5)	[214]
	AP	Western Turkey	1-hexacosanol (26.7), caryophyllene oxide (9.3), germacrene-D (9.3), α-selinene (8.7), Z-8-octadecen-1-ol acetate (7.1), 2,5-di-tertoctyl-p-benzoquinone (7.3), arachidic acid (6.0), tetracosane (4.5), heneicosane (4.4), heptacosane (4.3), 2-methyl-1-hexadecanol (3.3), octadecane (3.0), butyl phthalate (3.0)	[196]

cont.

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▶ **Table 12** *Continued*

Taxa		Origin	Main compounds	Ref.
B. nigra subsp. *foetida*	AP	Pisa, Italy	β-caryophyllene (25.1), germacrene D (24.2), 1-octen-3-ol (7.3), (*E*)-2-hexenal (6.1), α-humulene (4.3), caryophyllene oxide (4.2)	[215]
	AP	Urbino, Italy	β-caryophyllene (20.0), germacrene D (18.0), caryophyllene oxide (15.0), 1-octen-3-ol (6.8), (*E*)-2-hexenal (6.1), α-humulene (4.5), β-bourbonene (3.2)	[216]
	AP flowering	Urbino, Italy	β-caryophyllene (22.6), caryophyllene oxide (18.0), germacrene D (16.5), (*E*)-2-hexenal (6.5), 1-octen-3-ol (5.5)	[217]
	AP fruiting	Urbino, Italy	β-caryophyllene (21.8), caryophyllene oxide (20.5), germacrene D (13.1), (*E*)-2-hexenal (11.2), β-pinene (4.4), limonene (4.1), 1-octen-3-ol (3.5), linalool (3.5)	[217]
	AP	Nis, Serbia	(*E*)-phytol (56.9), germacrene D (10.0), β-caryophyllene (4.7), caryophyllene oxide (3.6), (E)-β-ionone (3.4)	[207]
	AP	Brac, Croatia	germacrene D (23.1), β-caryophyllene (20.3), caryophyllene oxide (6.2), caryophylladienol I (3.3), (*E*)-2-hexenal (3.1), hexadecanoic acid (3.1), α-humulene (3.0)	[218]
B. nigra subsp. *kurdica*	AP	Kurdistan, Iran	caryophyllene oxide (39.4), β-caryophyllene (24.9), germacrene D (7.6), 1-undecene (4.2), isoaromadendrene epoxide (3.2)	[219]
B. nigra f. *uncinata*	AP	Konya, Turkey	caryophyllene oxide (21.2), hexadecanoic acid (19.9), β-caryophyllene (18.9), germacrene D (4.6), hexahydrofarnesyl acetone (4.4), spathulenol (4.2), caryolphyllenol II (3.8); bicyclogermacrene (3.7)	[214]
B. pseudo-dictamnus	AP	Crete, Greece	caryophyllene oxide (22.4), phytol (11.9), γ-muurolene (11.4), (*E*)-caryophyllene (10.7), α-copaene (6.1), β-cucubene (5.3), hexahydrofarnesyl acetone (3.5)	[220]
B. saxatilis	AP	Amman, Jordan	linalool (14.6), caryophyllene oxide (11.0), acorenone (9.3), β-caryophyllene (7.9), germacrene D (7.6), 1-octen-3-ol (3.6), β-bourbonene (3.0)	[215]
	AP	Kfardin, Lebanon	linalool (11.2), (*E*)-β-caryophyllene (8.8), caryophyllene oxide (6.3), (*E*)-2-hexenal (5.6), hexadecanoic acid (4.9), (*Z,Z*)-9,12-octadecadienoic acid (3.4)	[218]
B. saxatilis subsp. *brachyodonta*	AP	Mersin, Turkey	(*E*)-β-caryophyllene (23.9), epi-bicyclosesqui-phellandrene (20.2), caryophyllene oxide (10.5), γ-elemene (5.5), thymol (4.1)	[221]
Ballota schimperi	L	Yemen	τ-cadinol (9.3), β-caryophyllene (8.8), bornyl formate (5.2), myrtenyl formate (3.8), spathulenol (3.2), β-selinene (3.0)	[222]
B. sechmenii		Turkey	linalool (5) (ratio (+)-linalool: (−)-linalool = 27 : 73)	[223]
B. undulata	AP	Naur, Jordan	germacrene D (19.1), bicyclogermacrene (11.6), viridiflorol (6.0), 1-octen-3-ol (3.5), *epi*-10-γ–eudesmol (3.1)	[215]
	AP	Kfardin, Lebanon	germacrene D (16.0), bicyclogermacrene (10.4), 9,12-octadecadienoic acid (5.3), hexadecanoic acid (4.5), dihydroactinidiolide (3.4)	[218]
O. fruticosa	AP culti-vated	El-Mansoura, Egypt	thymol (43.7), γ-terpinene (16.4), *p*-cymene (12.4), (*E*)-β-caryophyllene (9.5)	[224]
	AP	Sinai, Egypt	caryophyllene oxide (60.8), β-bisabolene (9.2), 4-decyne (5.1), α-*cis*-bergamotene (4.4), β-bourbonene (4.2), linalyl acetate (4.2)	[175]
O. integrifolia	Ls	North Shoa, Ethiopia	α-pinene (31.3), 1-octen-3-ol (11.8), β-caryophyllene (11.3), linalool (6.6), *cis*-β-ocimene (5.9), germacrene D (3.3)	[56]
O. michauxii	AP	Zagros, Iran	caryophyllene oxide (20.1), *trans*-verbenol (10.2), linalool (5.3) and humulene epoxide II (4.6)	[225]
	AP	Fars, Iran	dillapiole (23.9), 2-methylbenzofuran (12.9), α-pinene (8.1), δ-cadinene (6.1), 1-octen-3-ol (4.9), caryophyllene oxide (4.8), linalool (4.5), (*E*)-β-caryophyllene (3.6)	[226]
O. persica	AP	Fars, Iran	dillapiole (43.1), *trans*-verbenol (9.6), hexadecanoic acid (5.7), isospathulenol (4.5)	[227]
	L	Sistan, Iran	hexahydrofarnesyl acetone (14.3), *trans*-verbenol (10.2), geranyl acetone (6.5), pentadecane (5.9), hexadecane (5.9), α-pinene (4.5), *trans*-anethole (4.5), verbenone (3.5), 1-octen-3-ol (3.0)	[228]
	F	Sistan, Iran	α-pinene (13.6), *trans*-verbenol (9.2), linalool (6.8), hexadecane (5.5), caryophyllene oxide (4.8), pentadecane (4.6), *trans*-carveol (4.0), 1-octen-3-ol (3.8), geranyl acetone (3.7), heptadecane (3.3)	[228]
	flowering AP	Kerman. Iran	hexadecanoic acid (31.7), pentacosane (29.5), α-copaene-8-ol (5.9), hexadecanoic acid methylester (4.8), caryophyllene oxide (3.8), *trans*-damascenone (3.7)	[228]
	F	Kerman. Iran	α-pinene (17.2), 1-octen-3ol (13.4), cubenol (7.3)	[229]
	fruits	Kerman. Iran	diisooctyl phthalate (45.0), hexadecanoic acid (11.1)	[229]

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▶ **Table 13** The antioxidant activity of *Ballota* and *Otostegia* taxa.

Species	Origin	Sample preparation (plant part-solvent)	Test	Ref.
B. acetabulosa, *B. antalyanse*, *B. cristata*, *B. glandulosissima*, *B. inaequidens*, *B. larendana*, *B. latibracteolata*, *B. macrodonta*, *B. nigra* ssp. *anatolica*, *B. nigra* ssp. *foetida*, *B. nigra*, *B. nigra* ssp. *uncinata*, *B. pseudodictamnus* ssp. *lycia*, *B. rotundifolia*, *B. saxatilis* ssp. *brachyodonta*, *B. saxatilis*	Turkey	L: EtOAc, MeOH, W	FRAP (% inhib.): *B. antalyense* (1.34) MeOH extr., *B. saxatilis* ssp. *brachyodonta* MeOH extr. (1.28) *B. saxatilis* MeOH extr. (1.12); *B. antalyense* W extr. (1.24)	[230]
B. antalyense, *B. macrodonta*, *B. glandulosissima*, *B. larendana*, *B. pseudodictamnus*, *B. nigra* ssp. *anatolica*, *B. rotundifolia*, *B. saxatilis* ssp. *brachyodonta*, *B. saxatilis*	Turkey	L: EtOH/W 3 : 1	Superoxide anion formation quenching (SAFQ): IC_{50} 0.50 to 0.87 mg/mL; Liver rats lipid peroxidation (LO): not significant	[231]
B. antalyense, *B. macrodonta*, *B. glandulosissima*	Turkey	L: EtOH/W 3 : 1	SAFQ: 0.50, 0.51, 0.51	[231]
B. inaequidens, *B. glandulosissima*, *B. saxatilis*, *B. macrodonta*, *B. antalyense*	Turkey	L: EtOH/W 3 : 1	LO (mg/mL): 12 to 20 mg/mL	[231]
B. inaequidens, *B. glandulosissima*	Turkey	L: EtOH/W 3 : 1	LO: (mg/mL) 12 and 15	[231]
B. aucheri	Pakistan	AP: 70 % MeOH	DPPH: IC_{50} (µg/mL) 2.23	[232]
B. cinerea	India	AP: EtOH, then partition in $CHCl_3$, EtOAc, *n*-BuOH, W	DPPH: IC_{50} (µg/mL) 85–661; FRAP (mmolFe/g) 0.14–0.59; ABTS IC_{50} (µg/mL) 60–840; ORAC (TEAC mM) 8.55–36.0	[233]
B. deserti	Tunisia	L: MeOH, then partition in pet. ether, $CHCl_3$, EtOAc, BuOH	DPPH: IC_{50} (mg/mL) 0.85–2.50; ABTS: IC_{50} (mg/mL) 0.35–13, pet. Ether inactive	[25]
B. deserti	Algeria	EO	DPPH: IC_{50} µg/mL 35.9	[204]
B. deserti	Algeria	AP: CH_2Cl_2, MeOH, then isolat. compds: **114, 223, 227**	ABTS: IC_{50} (g/mmol) 0.14–3.50	[90]
B. deserti	Algeria	AP: CH_2Cl_2, MeOH, then isolat. compds: **76, 112–114, 139, 223, 227**	ABTS: EC_{50} (mol %) 0.09-> 0.50; CUPRAC: E‰ (L/mol/cm) 0.01–0.80; DPPH: EC_{50} (mol %) 0.39 – > 1.5, 9 and 12 oxidant or pro-oxidant	[89]
B. hirsuta	Algeria	L: W/MeOH 1 : 1, then partition in EtOAc, $CHCl_3$, *n*-BuOH	DPPH IC_{50} (mg/mL): 0.35 extr., 0.07 EtOAc, 0.26 $CHCl_3$, 0.12 *n*-BuOH	[234]
B. nigra	*ex vitro*	Shoots: MeOH	DPPH EC_{50} (mg/mL): 56.0–202.6, FRAP (µmol/g) 331.5–642.4; LPO (% inhb.) 20.97–36.05	[235]
B. nigra	Czech Republic	L: W	DPPH IC_{25} (µg/mL) 4.81; X/XO (µg/mL) 14.6; HClO scav. 80 % at 500 µg/mL; NO scav. IC25 (µg/mL) 122	[185]
B. nigra	France	L: 50 % EtOH, then isolat. compds: **186, 220, 221, 223, 227**	O_2^{2-} scav: IC_{50} (µg/mL) 30.6–149.0; H_2O_2 scav.: IC_{50} (µg/mL) 2.3–11.2; HClO scav.: IC_{50} (µg/mL) 1.5–9.3; OH rad. scav.: IC_{50} (µg/mL) 26.7–64.7.	[236]
			LDL-Ox: ED_{50} (µM) 1.0–9.5	[237]
B. nigra ssp. *anatolica*	Turkey	WP: PE, Ac, MeOH, W	ABTS (% inhib. at 100 mg/mL): 72–80	[196]
B. rotundifolia	Turkey	AP: MeOH	DPPH (µg/mg) 138.0; LPO (% inhib.): 35.97	[238]
B. undulata	Jordan	L: MeOH: compds: **116, 119, 147, 222, 223, 225, 227, 239**	ABTS, TEAC (mM) 0.68–1.67	[150]
B. pseudodictamnus, *B. acetabulosa*	Grecia	L: MeOH	Activity equal to α-tocopherol in Umezawa essay	[239]
O. integrifolia	Ethiopia	L: EtOAc, MeOH	DPPH: 82.9 MeOH, 32.7 EtOAc;	[240]
O. integrifolia	Ethiopia	EO	DPPH: EC_{50} (µL/mL) 5.32	[56]
O. limbata	Pakistan	WP: MeOH	DPPH: IC_{50} (mg/mL) 13.53–129.52; FRAP, (mM/mL) 88.86–334.27; LPO: ([% inhib.] 12.67–61.76).	[241]
O. limbata	Pakistan	AP: MeOH then solubilization in *n*-Hex, $CHCl_3$, EtOAc, BuOH, MeOH, W	DPPH: EC_{50} (µg/mL) 60–350; FRAP (mmol/mg) 5–41; ABTS, TEAC (µmol/g) 30–139	[242]

cont.

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▶ **Table 13** *Continued*

Species	Origin	Sample preparation (plant part-solvent)	Test	Ref.
O. persica	Iran	WP: MeOH, then solubilization in *n*-Hex and $CHCl_3$	LPO (% inhib.) 95.87 MeOH, 2.5 nHex., 1.9 $CHCl_3$	[158]
O. persica	Iran	EO	DPPH: IC_{50} (mM) 9.76	[228]
O. persica	Iran	EO in flowering EO in fruiting	DPPH: IC_{50} (µg/mL) 19.8, 29.2; LPO (% inhib.) 93.8, 63.0	[229]
O. persica	Iran	AP: MeOH	LPO (% inhib.) 95.87	[160]
O. persica	Iran	AP: MeOH, EtOAc	DPPH: IC_{50} 0.49 mg/mL for both	[141]
O. persica	Iran	L: 70% EtOH, then partition in PE, EtOAc, $CHCl_3$, *n*-BuOH, MeOH	DPPH: IC_{50} (µg/mL) 170 (EtOH) to 1580 (pet. Et.)	[243]

Similar hypolipidemic effects were observed in rabbits treated with the AP extract, in EtOH/water 7 : 3, of *B. undulata* from Jordan [286]. Two animal groups were treated with 400 mg of cholesterol/kg b.w. per day dissolved in 5 mL of coconut oil for 120 d; in 1 group 1.2 g/kg b.w. per day of the extract were added to the diet. A strong difference in lipidemic parameters was observed for the 2 groups: total cholesterol 807 versus 104, HDL 246 versus 40, phospholipids 252 versus 112, triglycerides 259 versus 74. Despite their scientific relevance, in our opinion, the eventual transfer of these findings on human trials might be strongly inhibited by the evident difficulty to orally administer a dose of 84 g/day of plant extract to an average weight human.

A potent antidiabetic effect was identified for the ethanolic extract of the *O. persica* AP from Iran [287]. The hematic glucose level of STZ-induced diabetic rats was normalized when animals received 200 to 500 mg/kg b.w. per day of the extract. At the maximum dose, the glucose level was lowered from 405–420 to 170–230 mg/dL, depending on the control time. Similar results were obtained by other authors [288] with the methanolic extract of this plant, also collected in Iran. In this case, the glucose level reduction observed in rat blood was accompanied by an increase in the insulin secretion in C187 pancreatic β-cells. Additionally, a reduction in lipidic oxidation was proved by the decrease in MDA values and the increase in GSH values. The ethanolic extract of *O. persica* was demonstrated to possess protective effects by preventing renal damage induced by ischemia/reperfusion induced in diabetic rats [289]. The hematic renal function indicators were ameliorated after treatment with 300 mg/kg b.w. of the extract for 2 wk: urea from 67.6 to 36.1, creatinine from 2.32 to 1.32, glucose from 378.6 to 147.2. Furthermore, kidney resection and tissue evaluation of the oxidative stress parameters (MDA, MPO, NO, SOD, and CAT) evidenced a beneficial effect in *O. persica* treated animals.

The antidiabetic activity of the AP of *O. persica* were assessed in different factions of the crude extract, following their solubility in PE, $CHCl_3$, EtOAc, *n*-BuOH, and MeOH [141]. The antioxidant activity was measured by DPPH method and was correlated to antidiabetic activity in mice. MeOH extract was effective in reducing hematic glucose with a 300 mg/kg b.w. dose. Both MeOH an EtOAc extract showed antioxidant activity with IC_{50} of 0.49 mg/mL for both. Finally, 4 compounds were isolated from the active extracts: chrysoeriol (**91**) from EtOAc, 6-methylapigenin (**77**), apigenin-7-*O*-β-D-glucopyranoside (**112**), and echinaticin (**138**) from the MeOH one.

The aerial part of *O. persica* also showed a potent antidiabetic effect when extracted in water at 40 °C [290]. Fasting blood sugar, insulin, and HOMA.IR (homeostasis model assessments for insulin resistance) were evaluated in STZ-induced diabetic mice after 10, 20, and 30 d of administration of up to 400 mg/kg b.w. of the extract. The indicator improvements were comparable to those reported in other studies, and total cholesterol and triglycerides were also significantly reduced: 95 versus 75 mg/dL for the former and 203 versus 71 for the latter. A reduction in the number and the mass of pancreatic β-cells was evidenced by histopathological visualization techniques.

The antidiabetic effect of *O. persica* (AP extracted in EtOH/H_2O 1 : 1) was also studied by stereological analysis of pancreas tissue in diabetic (STZ induction) Sprague-Dawley rats [291]. The oral administration of 500 mg/kg b.w. reduced blood glucose levels and insulin production, as reported in many other references. After 1 mo, the animals were sacrificed and pancreatic tissue was analyzed. A hypertrophic change in the remaining β-cells of the diabetic group was observed, accompanied by a reduction in pancreatic islet volume. These phenomena were significantly reduced in the animals treated with the extract.

B. aucheri extract (AP in 70% MeOH) [232] was effective in reducing postprandial hematic glucose increment in type II diabetic rats, while it was ineffective in type I diabetic animals. This antidiabetic activity was associated with a notable antioxidant activity determined in this sample (▶ **Table 13**).

Bone damage such as osteoporosis may constitute an important comorbidity in patients affected by mellitus diabetes. The aqueous extract of *O. persica* (Iran) was proven to act as a protection from bone damage in STZ treated diabetic rats [292]. Rats was treated orally with 200–450 mg/kg b.w. for 29 d. Then the left femoral and tibiofibular bones were dissected and evaluated histomorphometrically, while the right-side bones were removed for ash weight determination. The plant extract was able to significantly reverse the epiphyseal and metaphyseal trabecular width reduction observed in untreated animals. Additionally, the epiphyseal bone area/tissue were normalized with the utilization of the minimum extract dose. Ash weight was significantly lower in animals treated at 450 mg dose.

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▶ **Table 14** Antibacterial activity of *Ballota* and *Otostegia* taxa.

Species	Origin	Sample preparation (plant part: solvent)	Test	Target	Ref
B. acetabukosa	Turkey	L: EtOH 80%, W	MIC, MBC (µg/mL): 0.4–1.6; 3.2–12.5 (EtOH), 0.8–3.2, 6.3–12.5 W	*S. aureus*	[249]
B. acetabukosa	Turkey	L: EtOH	MIC (mg/mL) 32–1024; MBC (µg/mL) 64–1024.	*E. faecalis, E. coli, P. mirabilis, K. pnemoniae, P. aeruginosa*	[250]
B. africana	S. Africa	L: MeOH, W	MIC (µg/mL) 438	*K. pneumoniae, A. nauplii*	[251]
B. andreuzziana	Libya	WP: EtOAc, $CHCl_3$, BuOH, W	AD at 50, 100, 150 mg/mL (mm) 7–11	*S. aureus, B. subtilis, My phlei*	[148]
B. deserti	Algeria	EO L: MeOH	MIC biofilm formation EO (µL/mL) 25–80; MeOH (mg/mL) 3.25–25	*S. aureus* (ATCC 25923, ATCC 6538-P), *S. epidermidis, B. subtilis, B. cereus, S. mutans, M. luteus*	[204]
B. deserti	Algeria	AP: CH_2Cl_2, MeOH; then isolat. compds: **40, 223, 227**	MIC (µM): 46–162	*E. faecalis, P. aeruginosa, S. aureus*	[90]
B. inaequidens	Turkey	AP: Ac; isolat. compds: **5, 25, 79, 103, 105, 107, 108, 109**	MIC (µg/mL): 25–50	*S. aureus, B. subtilis, E. coli, P. aeruginosa*	[76]
B. nigra	Italy	S: EtOH	Quantification of δ-hemolysin. Response in the production of δ-hemolysin, indicating anti-QS activity in a pathogenic MRSA isolate. No inhibitory effect	*S. aureus*	[252]
B. nigra	Pakistan	S, L, R: EtOH then part. between W and *n*-Hex, EtOAc, $CHCl_3$, BuOH	AD at 5 mg/mL (mm) 8–30	*E. coli, S. aureus, P. mirabilis, K. pneumoniae, E. faecalis, S. typhi*	[253]
B. nigra	Serbia	S, L: EO	MIC (µg/mL): 2.5–5	*E. coli, S. aureus, B. mycoides, M. lysodeikticus, B. subtilis, K. pneumoniae, C. albicans*	[209]
B. nigra	France	shoots: 50% EtOH then isolat. compds: **220, 223, 227**	MIC (µg/mL): 64–128	*S. aureus, S. aureus* MRSA, *P. mirabilis*	[187]
B. nigra	Italy	WP: W	MIC, dose-dependent biofilm formation inhibition, max inhib. at 128 µg/mL	*S. aureus* MRSA	[254]
B. nigra spp. *anatolica*	Turkey	L: EtOH	MIC (µg/mL) 250–1000	*B. subtilis, B. cereus, S. aureus, E. coli, P. vulgaris, S. typhimurium, P. aeruginosa*	[255]
B. nigra spp. *anatolica*	Turkey	L: EtOH	AD at 50 µg/mL (mm) 10.0–19.2	*B. cereus, P. aeruginosa, K. pneumoniae, S. capitis, S. aureus, S. epidermidis, P. acnes, M. nonliquefaciens,*	[256]
B. nigra ssp *foetida*	Italy	EO	MIC, MBC (mg/mL): 3–7	*E. coli, E. cloacae, P. aerouginosa, F. fluorescens, S. aureus, S. epidermidis*	[216]
B. pseudo-dictamnus	Pakistan	S, L, R: EtOH then part. bet. W/*n*-Hex, EtOAc, $CHCl_3$, BuOH	AD at 2 µg/mL (mm) 0.8–20	*E. coli, S. aureus, P. mirabilis, K. pneumoniae, E. faecalis, S. typhi*	[257]
B. pseudo-dictamnus	Greece	EO	MIC (mg/mL) 0.45–10.15, > 20 for *E. coli*	*S. aureus, S. epidermidis, E. coli, E. cloacae, K. pneumoniae, P. aeruginosa*	[220]
B. rotundifolia	Turkey	WP: MeOH then the extract was split in W-soluble and W-insoluble fractions	MIC (µg/mL): > 72	*S. pneumoniae, B. cereus, A. lwoffii, E. coli, K. pneumoniae, C. perfringens*	[238]
B. saxatilis	Turkey	F: Ac: then isolat. compds: **5, 18, 25**	MIC (µg/mL): 25–50	*S. aureus, S. faecalis, E. coli, P. aeruginosa, K. pneumaniae.*	[80]
B. saxatilis ssp. *brachyodonta*	Turkey	EO	MIC (µg/mL): 25–50	*E. coli, E. feacalis, B. subtilis, S. thyphimurium, S. aureus, S. epidermidis, K. pneumoniae*	[221]
O. fruticosa	Egypt	EO	MIC (µg/mL): 1.5–6	*B. subtilis, S. aureus, E. coli, S. epidermidis, S. faecalis, K. aerogenes*	[224]
O. fruticosa ssp. *schimperi*	Yemen	EO	MIC (µg/mL): 310–1250	*B. cereus, S. aureus, E. coli, P. aeruginosa*	[222]
O. integrifolia	Ethiopia	L: 80% MeOH, $CHCl_3$	MIC (mg/mL): 0.312	*M. tuberculosis*	[258]

cont.

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▶ **Table 14** *Continued*

Species	Origin	Sample preparation (plant part: solvent)	Test	Target	Ref
O. integrifolia	Ethiopia	EO	MIC (mg/mL) 5–100	*E. coli* 18/9, *E. coli* ATCC 10536, *E. coli* CD/99/1, *E. coli* K88, *E. coli* RP4, *E. coli* VC Sonawave 3 : 37 C, *P. aeruginosa*, *S. boydii*, *S. dysentery*, *S. flexneri*, *S. soneii* 1, *S. soneii* BCH 217, *V. cholera*, *B. subtilis*	[56]
O. limbata	Pakistan	WP: 70 % EtOH. then ext. solubilized in DMSO, EtOH, MeOH	MIC (mg/mL): 0.2–5	*B. subtilis*, *L. monocytogenes*, *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* spp.	[259]
O. persica	Iran	AP: MeOH	MIC (mg/mL): 0.5–2	*E. coli*, *B. subtilis*, *S. aureus*, *S. epidermis*, *P. aeruginosa*, *S. typhi*, *K. pneumonia*, *A. niger*	[260]
O. persica	Iran	AP: 70 % EtOH, *n*-Hex, $CHCl_3$, MeOH	MIC (mg/mL): 1.25–25	*E. coli*, L. *monocytogen*, *E. faecalis*, *S. aureus*, *S. epidermidis*, *B. subtiltis*, *P. aeruginosa*, *Salmonella* spp. *Klebsiella* spp.	[261]

The Ethiopian plant *O. integrifolia*, in particular the leaf extract in 80 % MeOH, was also effective in contrasting diabetes in mice and rats [293]. STZ induced diabetic mice receiving doses from 100 to 400 mg/kg b. w. of extract displayed time-dependent hypoglycemic effects. After 4 h, the dose of 200 mg reduced the hematic glucose from 375 to 159 mg/dL.

Three extracts were obtained from the AP of *B. cinerea* (India) by brewing them in PE, EtOAc, and MeOH [294]. They were active in reducing blood glucose levels in diabetic rats both with acute (after 4 h) and with chronic (after 21 d) alloxana-induced disease. Total reduction of glucose reached values (36–42 %) comparable to the standard antidiabetic drug glibenclamide. Other authors [267] reported slightly different values for the activity of the same extracts, together with the EtOH extract, assessed in the reduction of hematic glucose in STZ-induced diabetic rats: from 18.2 to 23.4 % reduction after 24 h at 100 mg/kg b. w. Furthermore, similar results in reducing murine glycemia were obtained with the butanol and water extract of the same taxon [233]. In the last study, the lipidic profile, the hepatic glycogen content and the pancreatic parameters (SOD, GSH, and PGx) were also evaluated after 15 d of extract treatments at 50 mg/kg b. w. Almost all of the parameters were normalized as compared to standard values, and these beneficial effects were confirmed by the histopathological evaluation of pancreatic and hepatic tissue dissections. Take note that the dose of extract implemented in this study is significantly lower than the average doses normally utilized in similar contexts.

4-Methoxybenzo[*b*]azet-2(1H)-one (**214**) and 3*β*-hydroxy-35-(cyclohexyl-5′-propan-7′-one)-33-ethyl-34-methyl-bacteriohop-16-ene (**178**), isolated from the aerial part of *B. cinerea* (India) [182], significantly reduced the blood glucose level in alloxan-induced diabetic rats at the dose of 10 mg/kg b. w. administered orally.

An interesting protective effect for hyperlipidemia was investigated for the aqueous extract of *B. arabica* (syn. *L. urticifolia*) in a Triton WR-1339 induced hyperlipidemic rat model [295]. The administration of a 100–400 mg/kg b. w. dose for 24 h was able to restore normal values of plasma lipidic parameters, total cholesterol, TG, LDL, VLDL, and to significantly raise the HDL level.

Other bioactivities *in vivo*

The fruit extract of *B. undulata* obtained in EtOH/water 7 : 3 was shown to be effective as a fertility controller in Albino rats [296]. The effects were time dependent: after a treatment of 4 wk at 15 mg/kg b. w. per day, the numbers of pregnancies was not reduced significantly, while only a slight reduction in embryo and ovarian weights was observed. On the contrary, when the treatment was prolonged until 12 wk, the percentage of embryo implantation and pregnancies with respect to the controls was statistically relevant.

The extract of *O. persica* AP in MeOH was tested for its healing promoting activity in the skin of Wistar rats [297]. The healing process of burns provoked in the dorsal part of animals was accelerated by the application of a ointment in which the extract was dispersed. The histological evaluation evidenced an increase in fibroblast proliferation, angiogenesis and re-epithelialization that improved in a 5- to 14-d time range.

Ischemia-reperfusion is a dangerous syndrome that can cause severe injuries to remote organs, due to multiple effects, including the increase in reactive oxygenated radicals and general inflammation conditions. The ethanolic extract of *O. persica* (Iran) demonstrated protective effects toward renal injury in rats suffering of a hindlimb ischemia reperfusion surgically induced by clamping the femoral artery [298]. Reperfusion induced kidney damage including the increase of water uptake, creatinine excretion rate, and kidney/body weight. The animals treated with 300 mg/kg b. w. of extract 2 d before intervention had the above-mentioned renal functionality parameters at levels comparable with the negative control.

The antihypertensive effect of the AP extract (70 % EtOH) of *O. persica* was proven in Wistar rats suffering from dexamethasone-induced hypertension [299]. The systolic pressure increase from 115 to 143 mmHg was completely suppressed by a dose of 400 mg/kg b. w. per day of the extract, administered 2 d before starting the dexamethasone treatment. The hematic H_2O_2 and FRAP values increased by dexamethasone were also normalized in the animals receiving the plant brew.

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▶ **Table 15** Antifungal activity of *Ballota* and *Otostegia* taxa.

Species	Origin	Sample preparation (plant part: solvent)	Test	Target	Ref.
B. acetabulosa	Turkey	L, R: 50% EtOH	MIC (mg/mL) 1.56–25.0	*C. albicans, C. tropicalis, C. guilliermondii, Cryptococcus neoformans, C. laurentii*	[263]
B. deserti	Algeria	EO L: MeOH	MIC biofilm formation EO (µL/mL) 25; MeOH extr, (mg/mL) 12.5	*C. albicans*	[204]
B. inaequidens	Turkey	AP: Ac; then isolat. compds: **5, 25, 79, 103, 105, 107, 108, 109**	MIC (µg/mL) 3.1–12.5	*C. albicans, C. crusei*	[76]
B. nigra	Paikstan	S, L, R: EtOH then partition between W/n-Hex, EtOAc, $CHCl_3$, BuOH	Agar tube diluition, results reported as inhibition "positive" or "negative"; crude extrat always positive at 2 mg/mL	*A. niger, A. flavus, A. fumigatus, F. solani*	[253]
B. nigra ssp. *anatolica*	Turkey	L: EtOH	MIC (µg/mL): 500–1000	*C. albicans, D. hansenii, K. fragilis, R. rubra*	[255]
B. nigra ssp *foetida*	Italy	EO	MIC (mg/mL) 5.5; MBC (mg/mL) 15.0	*C. albicans, C. glabrata, C. tropicalis*	[216]
B. pseudodictamnus	Pakistan	S, L, R: EtOH then partition between W/*n*-Hex, EtOAc, $CHCl_3$, BuOH	Agar tube dilution, results reported as inhibition "positive" or "negative" at 2 mg/mL	*A. niger; A. fumigates, A. flavus; F. solani*	[257]
B. pseudodictamnus	Greece	EO	Not active	*C. albicans, C. tropicalis, C. glabrata*	[220]
B. rotundifolia	Turkey	WP: MeOH then the extract was split in W-soluble and W-insoluble fractions	MIC (µg/mL) > 72	*C. albicans, C. krusei*	[238]
B. saxatilis	Turkey	L: Ac then isolat. compds: **5, 18, 25**	Agar diluititon MIC (µg/mL): 1.5–3.1	*C. albicans*	[80]
B. saxatilis ssp. *brachyodonta*	Turkey	EO	MIC (µg/mL): 25	*C. albicans* (clinic strain), *C. parapsilosis*	[221]
B. undulata	Egypt	L, S, F: EtOH, EtOAc, $CHCl_3$, *n*-Hex	MIC (mg/mL): 25 – > 150	*T. rubrum, T. tonsurans, C. albicans, C. tropicum, P. lilacinus, P. variotii, S. bervicaulis*	[264]
O. integrifolia	Ethiopia	EO	MIC (µg/mL): 50–100	*A. niger, C. albicans, P. funiculosum, P. notatum*	[56]
O. fruticosa	Egypt	EO	MIC (µg/mL): 6.0, 16.0	*C. albicans, S. cerevisiae*	[224]
O. limbata	Paikstan	WP: MeOH, then partition in *n*-Hex, $CHCl_3$, EtOAc, BuOH	MIC (mg/mL) 0.18–1.5	*S. setubal, P. pickettii, S. aureus, M. luteus*	[265]
O. persica	Iran	AP: MeOH	MIC (mg/mL): 1.0	*C. albicans*	[260]

Anti-malarial activity

A significant antimalarial effect in *Plasmodium berghei* Vinke & Lips-infected mice was disclosed for *O. integrifolia* collected in Ethiopia [300]. Mice were administrated with 200, 400, and 800 mg/kg b.w. doses of the leaf extract prepared in chloroform, MeOH, and water. The survival of the animals treated with polar extract was dose-dependent and significantly higher than that of the negative control (10.5 vs. 7.5 d of H_2O ext. at max. dose; 13.5 vs. 7 for MeOH ext.). General lack of toxicity was proven until reaching a 2000 mg/kg b.w. dose. Also in this case, the very high dose of extract employed may be an obstacle for possible developments toward application to humans. However, a study appearing in the literature in the same year [101] resulted in the bioguided isolation of the labdane diterpene otostegindiol (**43**) from the methanolic extract of *O. integrifolia* leaves. This compound showed chemosuppressive properties against *P. berghei* with a maximum suppression ratio of 73.16% at 100 mg/kg. Additionally, the EtOH extract of the aerial part of Iranian *O. persica* [301] demonstrated antimalarial activity in *P. berghei* infected mice with ED_{50} of 45 mg/kg b.w. Furthermore, an interesting synergistic effect was observed when CQ-sensitive animals were treated with a combination of this drug and the plant extract; for example, a combination of 70% of the ED_{50} of CQ with 30% of extract caused a 26% increase in the mean effective dose.

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The effective antiprotozoal activity against another relevant malarial parasite, *Plasmodium falciparum* Welch, was disclosed in both the PE and the chloroform extracts of *B. cinerea* from India [302]. The IC_{50} values for the 2 materials were 4.39 and 1.84 µg/mL, respectively.

Hepatoprotective effects

The AP extract (80% MeOH) of *O. persica* collected in Iran [303] was effective in strongly reducing liver damage in CCl_4 intoxicated rats (2.5 mg/kg b.w.). After administrating 400 mg/kg b.w. of extract, hematic liver damage parameters were significantly ameliorated with respect to untreated animals: ALT 13%, AST 11.6%, plasma MDA 6.7%, liver MDA 11.4%, liver GSH + 21%. Histological evaluation of liver sections demonstrated the prevention of tissue degradation in treated rats. A similar protective effect was described for the aqueous extract of the AP of *B. glandulosissima* from Turkey [245]. Liver damage indicators in the blood of CCl_4-treated rats (0.8 mL/kg b.w.) were reduced significantly with 100 mg/kg b.w. of extract: AST 59%, ALT 47%, ALP 43%, bilirubin 47%. The efficacies of the 2 above-cited treatments are hardly comparable considering the differences in applied dose intoxication, in the extraction procedure and in the feeding procedures of the animals involved in these studies. Similar protective effects on the liver were found in the AP extract (70% MeOH) of *O. persica* collected in Iran [304] administrated to rats at 80–120 mg/kg b.w.

The hepatoprotective effect of *B. cinerea* (syn. *Roylea elegans* Wall. ex Benth.) collected in India was assessed for the AP extract obtained in EtOH/H_2O 1:1 in a CCl_4 and paracetamol toxicity induced model in rats [305]. Hepatic damage was evaluated by several blood parameters, such as SGOT, SGPT, ALP, and TB, after treatment with 100–400 mg/kg b.w. of extract for 7 d. Also, the liver oxidative stress indicators GSH and TBARS were followed. The pathological displacement of all of the indicators was reduced in a dose-dependent fashion and complete normalization occurred at the dose of 400 mg.

Enzymatic activity modulation

There are a number of investigations aimed at evaluating the plants from *Ballota* and *Otostegia* genera as a source of useful bioactive compounds isolated from the complex blend of their secondary metabolites. The extract of *O. limbata* root in MeOH led to the isolation and identification of 3 new tricyclic *cis*-clerodane diterpenes: limbatolide A (**64**), limbatolide B (**65**), and limbatolide C (**66**) that were assessed of their inhibitory potential against acetylcholinesterase (AChE; EC 3.1.1.7) and butyrylcholinesterase (BChE; EC 3.1.1.8). The inhibition activity was higher for the latter enzyme (IC_{50} 22.3, 17.5 and 14.2 µM, respectively) than for the former (IC_{50} 38.5, 47.2, and 103.7 µM) [112]. These enzymatic systems were also the targets of another similar work concerning the isolation of 6 clerodane tricyclic diterpenes from the chloroform extract of *B. limbata* [107]: ballatenolide A (**59**), 15-methoxypatagonic acid (**71**), patagonic acid (**72**), and limbatenolides A–C (**54–56**). All of the compounds showed inhibitory activity with BChE with IC_{50} values ranging from 24.9 to 51.0 µM, lower than the standard inhibitor galanthamine (8.5 µM). The first group of 3 compounds also showed a moderate inhibitory activity with AChE with IC_{50} values between 50.0 and 102 mM (galanthamine 0.50 µM). The inhibition activity toward the 2 enzymatic systems was also assessed with the MeOH extract of the aerial part of *B. deserti* from Algeria [204], obtaining moderate IC_{50} values: 277.4 µg/mL for AChE and 93.3 µg/mL for BChE.

Ballotenic acid (**60**) and ballodiolic acid (**62**) were isolated from the chloroform soluble fraction of the MeOH extract of *B. limbata* [110] and displayed inhibitory potential against lipoxygenase enzyme in a concentration-dependent fashion with IC_{50} values of 99.6 µM and 38.3 µM, respectively.

Furthermore, the crude *n*-Hex extract of *B. nigra* subsp. *kurdica* [306] from Iran was investigated for its possible tyrosinase inhibitory activity by the colorimetric Tyrosinase inhibition assay (IC_{50} = 3.67 µg/mL); however, no attempt was made to isolate individual active molecules.

Tyrosinase was also effectively inhibited by 2 compounds isolated from the AP extract of *B. cinerea* from India [182]: 4-methoxybenzo[*b*]azet-2(1H)-one (**214**) and 3*β*-hydroxy-35-(cyclohexyl-5′-propan-7′-one)-33-ethyl-34-methyl-bacteriohop-16-ene (**178**) with inhibition rate of 83.0 and 58.2%, respectively, at 100 µM. These compounds were also effective inhibitors of *α*-glucosidase (78.5% and 58.4%). This inhibitory activity is related to the above discussed antidiabetic activity *in vivo* of these compounds. The *α*-glucosidase and *β*-glucosidase reduction activities were evaluated in a study on the antidiabetic activity *in vitro* and *in vivo* of some extracts of *B. cinerea* from India [294]. Three fractions were found more active, respectively, obtained with PE, EtOAc, and MeOH; their activity reduction power ranged about from 55 to 80%, with the MeOH extract being the most active. In another work [267], these extracts were tested in an *in vitro* inhibitory activity test against protein tyrosine phosphatase-1B, showing results ranging from 39 to 65% inhibition at 100 µM.

α-Amylase, an enzyme involved in saccharide metabolism which is believed to possess preventive properties for type II diabetes, is strongly inhibited by polyphenolic compounds [307]. For this reason, the inhibitory activity of the extracts of *O. persica* was evaluated in association with the antioxidant activity (DPPH test, see ▸ **Table 13**) [243]. The initial crude extract obtained in EtOH was then partitioned in solvents of different polarities: PE, EtOAc, $CHCl_3$, *n*-BuOH, EtOH. The enzymatic parameters were measured for all of the fractions: inhibition rate from 53.3 (pet. Ether) to 99.4% (EtOAc). The author attempted to relate the total phenolic content of the extracts both with the antioxidant and the enzyme inhibition activity.

The 2 new flavonoidal glucosides leufolins A (**163**) and B (**152**) isolated from *B. arabica* (syn. *L. urticifolia*) have shown to be potent inhibitors of BChE enzyme (IC_{50} values 1.6 and 3.6 µM, respectively) when compared to serine, used as a positive control (IC_{50} 0.93 µM). On the other hand, very weak activity was observed against acetylcholinestrase (IC_{50} values 74.5 and 72.3 µM, respectively), compared to eserine (IC_{50} = 0.04 µM) [171]. The new steroid leucisterol (**179**), also isolated from the same species, showed potent inhibitory activity against butyrylcholinesterase enzyme (IC_{50} = 3.2 µM). [181].

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Conclusions

In this review a complete recognition of the volatile and not volatile secondary metabolites occurring in the *Ballota* and *Otostegia* genera has been carried out. The ^{13}C NMR data of diterpenes reported in literature have been collected for comparison purposes in structural determination. Some relevant studies on several biological activities have been reported that include antioxidant, anti-inflammatory, antibacterial, antifungal, antitumor, and antidiabetic.

Acknowledgements

This work was supported by grant from MIUR-ITALY PRIN 2015 (Project N. 2015MSCKCE_003) and PRIN 2017 (Project N. 2017A95NCJ).

Conflict of Interest

The authors declare that they have no conflict of interest.

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