

# A Review of the Phytochemistry, Traditional Uses, and Biological Activities of the Genus *Ballota* and *Otostegia*<sup>1</sup>

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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 andreuziana* 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*

<sup>1</sup> 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.

## 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	glutathione
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
<i>n</i> -Hex	<i>n</i> -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 lipoproteins
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 schenikovii* 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.

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

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

## 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,

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 “kattekruiie.” 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” (ጥንጅት), 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. fruticososa* has been similarly used against diarrhea [46], and the latter also against ascariasis [46] and tonsillitis [48].

*O. fruticososa* 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.

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

Species	Vernacular names	Area	Use	Ref
<i>B. acetabulosa</i>	boz ot	Aydin, Turkey	stomach ailments, abdominal pain	[11]
		Balikesir, Turkey	hemorrhoid treatment	[12]
<i>B. africana</i>	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]
<i>B. arabica</i>	kubo, goma	Baluchistan, Pakistan	abortifacient, astringent, stimulant, hemostatic, anthelmintic, diuretic	[16]
<i>B. aucheri</i>	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]
<i>B. cinerea</i>	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]
<i>B. deserti</i>	telheret, meriout	Central Sahara	respiratory diseases, fever, colics, colds, cough, digestive troubles, helminthiasis, nausea	[23, 24]
		Tunisia	asthma, diabetes, diuretic	[25]
<i>B. hirsuta</i>	uarimsa, tougan-n'if-zi, tifziguiyin	High Atlas, Morocco	general health, gastrointestinal, gynecological, pediatric	[26]
		West Algeria	contusion, injuries and rheumatic pain	[27]
<i>B. lanata</i>		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]
<i>B. nigra</i>		Sharr Mt., Macedonia	digestive	[30]
		Moldova	sedative, antispasmodic stimulant, vermifuge	[31]
	crna kopriwa	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 kopriwa	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]
<i>B. nigra</i> L. subsp. <i>anatolica</i>	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]
	pembereikli, oğul otu, ari oto	Gönen, Turkey	burns, wounds, headache	[42]
	grip otu	Kırklareli, Turkey	cold, flu	[43]
<i>O. fruticosa</i>		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.

► **Table 2** Continued

Species	Vernacular names	Area	Use	Ref
<i>O. integrifolia</i>	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]
<i>O. limbata</i>	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 ophthalmia in man	[63]
	sassa	Chon. Karak, Pakistan	treatment of children's gums and for ophthalmia 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, ophthalmia and gums diseases	[68]
	Koribooti	Himalaya	wound healing	[69]
<i>O. persica</i>	golder	Baluchistan, Iran	diabetes, rheumatism, cardiac distress, reducing palpitation, hypertension, laxative, carminative, antipyretic, cold, hyper lipidemia, gastric discomfort, parasite repellent, sedative, headache	[17]
<i>O. tomentosa</i>		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 $\alpha$ -acetoxyroyleanone (**73**) and coleon A (**74**), belonging to abietane diterpenoids, and 7,8 $\beta$ -epoxymomilactone-A (**75**), belonging to pimarane diterpenoids, 3 main carbon-skeletons occur: labdane, hispanane, and clerodane.

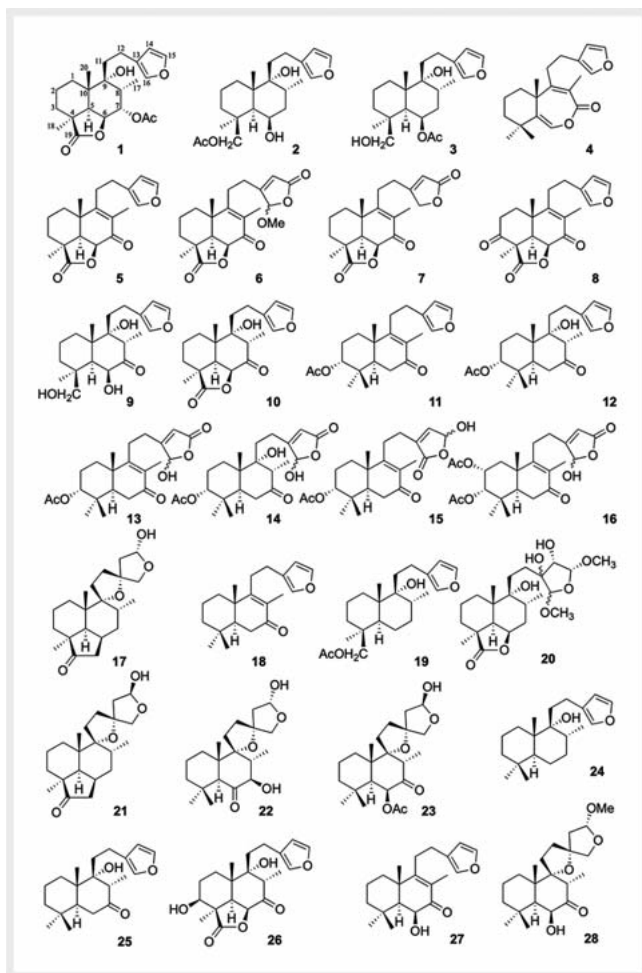
The labdane diterpenoids (**1–50**) (► **Figs. 1** and **2**) are characterized by some interesting structural features. They all belong to a normal labdane stereochemical series, although Gray et al. [118] claimed, based on the optical rotation, that compound **27** had an *ent*-labdane skeleton. The 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  $\gamma$ -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.

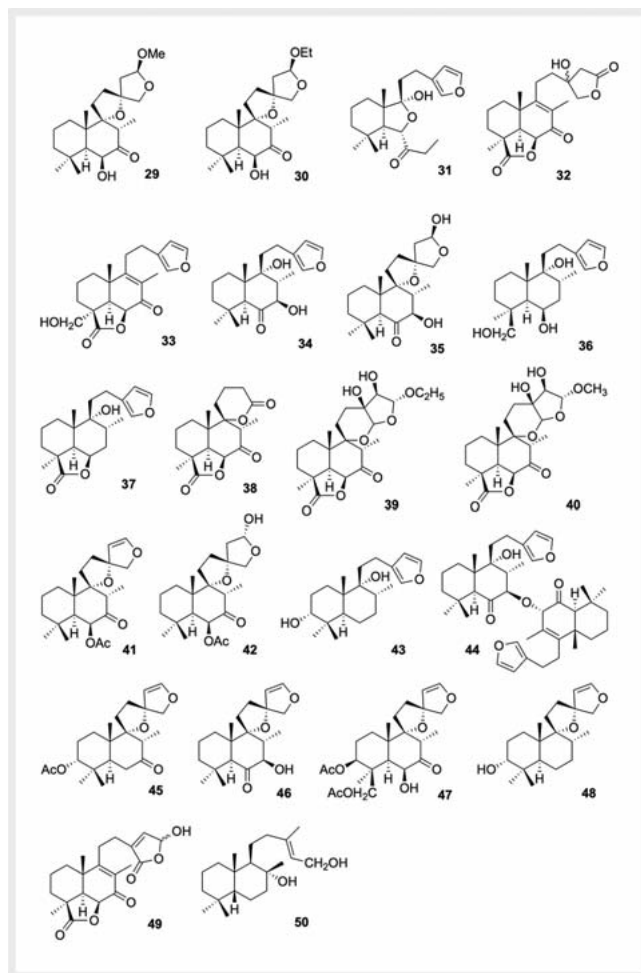
The decalin moiety contains some constant functional features: the decalin junction is always *trans* and the methyl groups (C-17) in position C-8; when it is not present, a C-8/C-9 double bond is always  $\alpha$ -orientated. In the majority of the structures, C-6 and C-7 show oxygenated functions and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

Hispanane-type diterpenoids (► **Fig. 3**) are a scarce group of natural diterpenoids that exhibits a 6/7/6 tricyclic 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*- $\beta$ -glucoside [121] (from *Salvia digitaloides* Diels), and



► 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 ( $\beta$ -H 5 and  $\alpha$ -CH<sub>3</sub> 20) [122], the absolute configurations of any of the hispananes have been not determined. In this review, we will report the configuration depicted in the original papers ( $\alpha$ -H 5 and  $\beta$ -CH<sub>3</sub> 20). The plausible biosynthetic pathway was speculated as a pimarane [121] or ladbane way [123].

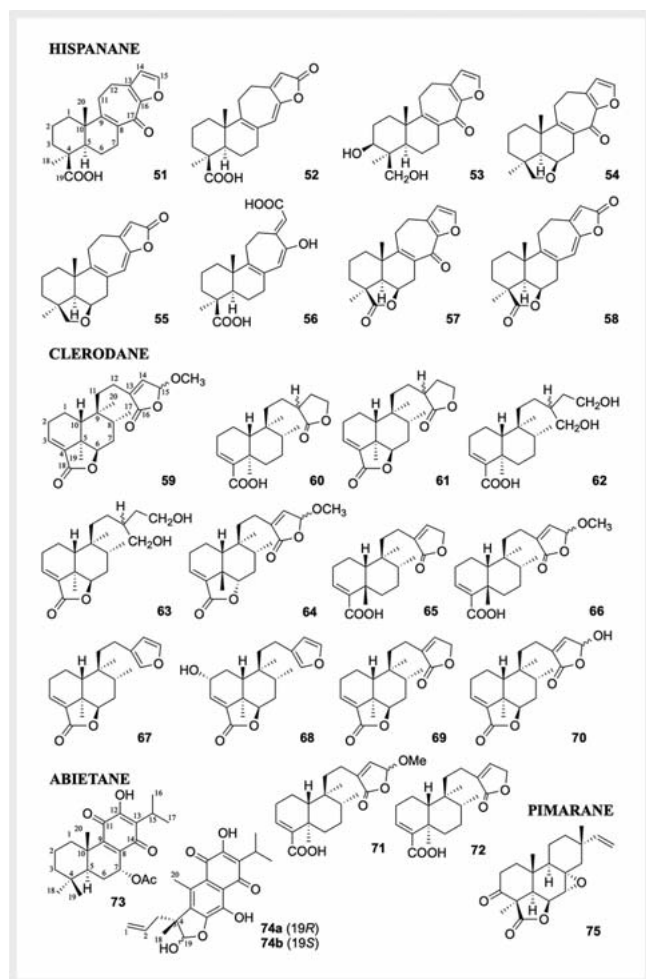
Clerodane diterpenoids (► Fig. 3) showed, differently from ladbanes, both a *trans* junction and a *cis* junction of the decalin moiety (64–66). Apart from ballodiolic acid (62) and ballodiolic acid A (63), all the other compounds showed the C-13/C-16 as furane ring (67, 68) or  $\gamma$ -lactone. Common 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 <sup>13</sup>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*- $\beta$ -D-glucopyranoside (112) (9 taxa), ladanein (79) (8 taxa), apigenin (75) (6 taxa), luteolin-7-*O*- $\beta$ -D-glucopyranoside (116) (6 taxa), and rutin (124) (6 taxa).



► 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*- $\beta$ -(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: triterpenoids, 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 Pialt [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 ballotetriside (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  $\beta$ -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



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

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

continued

► Table 3 Continued

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

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<sub>2</sub>O<sub>2</sub>, HClO, and OH radical. All of the compounds were found to be active, inhibiting the development of oxygenated species to various degrees; only ballotetroside (**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<sub>50</sub> 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<sub>2</sub>O for *B. nigra* (129.5 µg/mL) and the one obtained in CHCl<sub>3</sub> 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<sub>4</sub>SCN test comparable to that of α-tocopherol (95.87%). On the other hand, the fractions soluble in *n*-Hex and CHCl<sub>3</sub> 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<sub>2</sub>O<sub>2</sub> and evaluated by the cell viability assay (MTT), intracellular and extracellular total

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

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

peroxides test, and FRAP. The extract significantly reduced the effect of H<sub>2</sub>O<sub>2</sub> in a dose-dependent fashion (50–250 µg/mL).

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<sub>3</sub>, EtOAc, *n*-BuOH, MeOH, and H<sub>2</sub>O, and total content in phenolic compounds and flavonoids was determined. The EtOAc fraction resulted the one with the highest antioxidant power (EC<sub>50</sub> TPPH test 60.9 µg, total phenolic compounds 1119 mg), even if the higher phenols content was found in *n*-Hex (3908 mg, EC<sub>50</sub> 226.1 µg) and 1-butanol (3037 mg, EC<sub>50</sub> 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

▶ **Table 5** <sup>13</sup>C-NMR 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.	
<b>Labdane skeleton</b>																								
<b>1</b> 7 $\alpha$ -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]
<b>2</b> 6-acetyl-marrubenol	Not reported in literature																							
<b>3</b> 19-acetyl-marrubenol	Not reported in literature																							
<b>4</b> 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]
<b>5</b> 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]
<b>6</b> 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]
<b>7</b> 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]
<b>8</b> 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]
<b>9</b> 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]
<b>10</b> 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]
<b>11</b> calyene	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]
<b>12</b> 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]
<b>13</b> 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]
<b>14</b> 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]
<b>15</b> 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]
<b>16</b> 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]
<b>17</b> 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]
<b>18</b> dehydrohispanolone (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]
<b>19</b> 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]
<b>20</b> 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]
<b>21</b> 15- <i>epi</i> -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]
<b>22</b> 15- <i>epi</i> -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]
<b>23</b> 15- <i>epi</i> -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.

► 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-hydroxy/labda-13(16), 14- diene	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	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	3 $\beta$ -hydroxyballotri- none	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	6 $\beta$ -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	6 $\beta$ -hydroxy-15 $\alpha$ -methoxy-9 $\alpha$ ,13,15,16-bis-epoxy-labd-7-one	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature
29	6 $\beta$ -hydroxy-15 $\beta$ -methoxy-9 $\alpha$ ,13,15,16-bis-epoxy-labd-7-one	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature
30	6 $\beta$ -hydroxy-15 $\beta$ -ethoxy-9 $\alpha$ ,13,15,16-bis-epoxy-labd-7-one	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature	Not reported in literature
31	9 $\alpha$ -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-hydroxyballonigrillide	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	marrubanol	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	marrubinin	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	marrulibacetal	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	marrulibacetal 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.

▶ Table 5 Continued

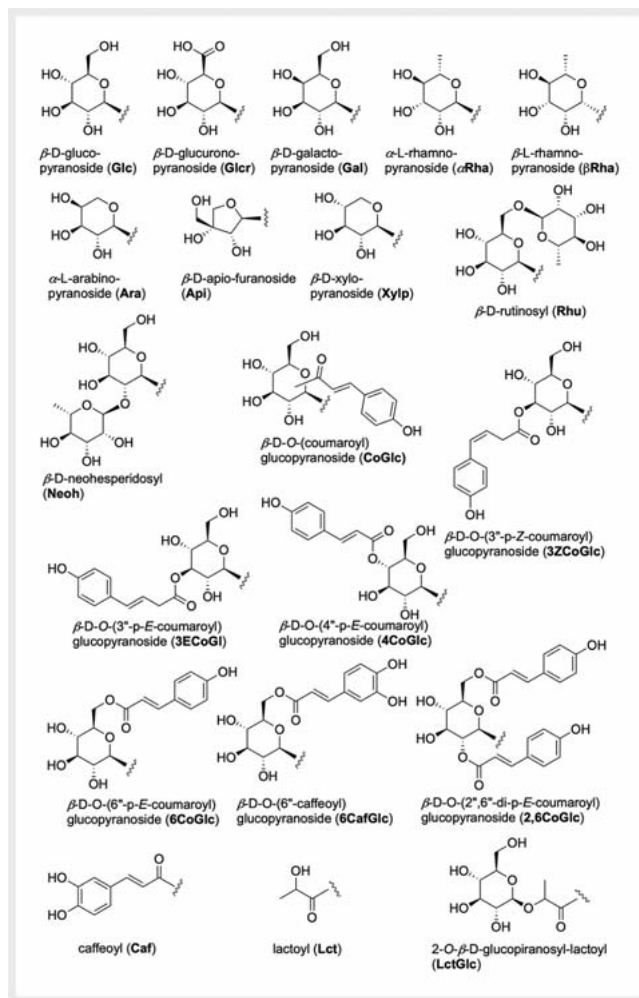
Skeleton numbering	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	1'	2'	Ref.	
44	persianone	31.5	18.2	42.3	32.3	57.4	210.7	65.0	50.5	77.0	48.7	43.6	21.5	124.9	110.7	143.0	138.6	13.1	32.7	22.3	18.0			[74]
		36.5	18.7	42.2	32.1	58.3	211.3	67.9	128.1	144.4	45.1	29.2	25.4	125.1	110.7	142.8	138.5	16.5	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	preleoisobirin	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]
	<b>Hispanane skeleton</b>																							
51	hispannic acid <sup>a</sup>	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 <sup>a</sup>	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]
	<b>Clerodane skeleton</b>																							
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.																						

▶ 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	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	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]	
<b>Abietane skeleton</b>																								
73	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	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	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]	
<b>Pimarane skeleton</b>																								
75																								

Not reported in literature

<sup>a</sup>The spectra were recorded as methyl ester derivative.

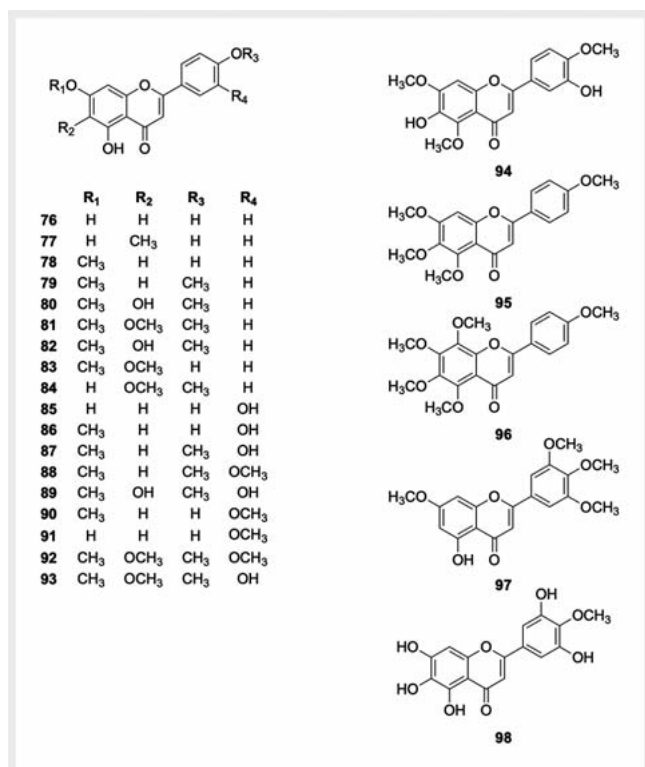


▶ Fig. 4 Structures of sugars and acyl moieties.

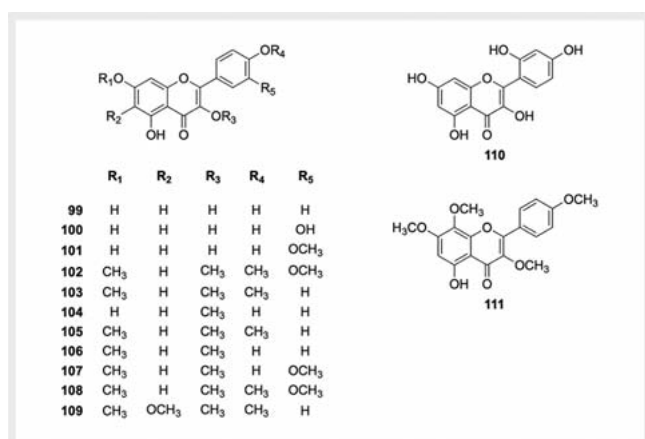
rats with a 7 week treatment of STZ. Afterward, the plasma concentration of malondialdehyde (MDA), co-enzyme Q<sub>9</sub>,  $\alpha$ - and  $\gamma$ -tocopherol were measured. A normalization in MDA values was observed in animals treated with 60 mg/kg b.w. of compound 139, while the Q<sub>9</sub> and  $\gamma$ -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-



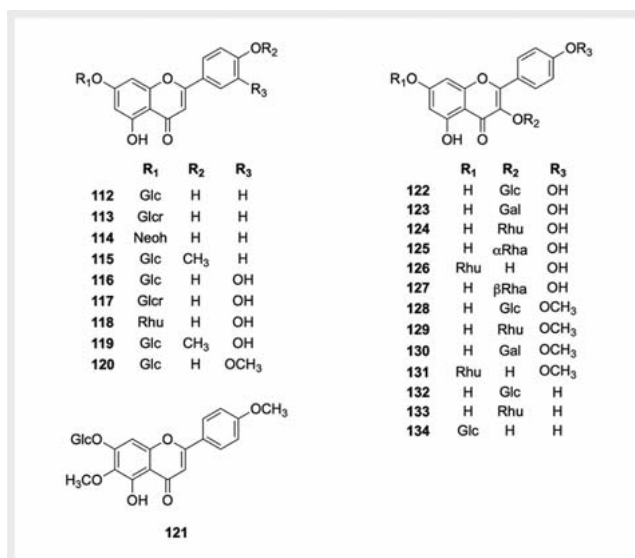
► Fig. 5 Structures of flavones.



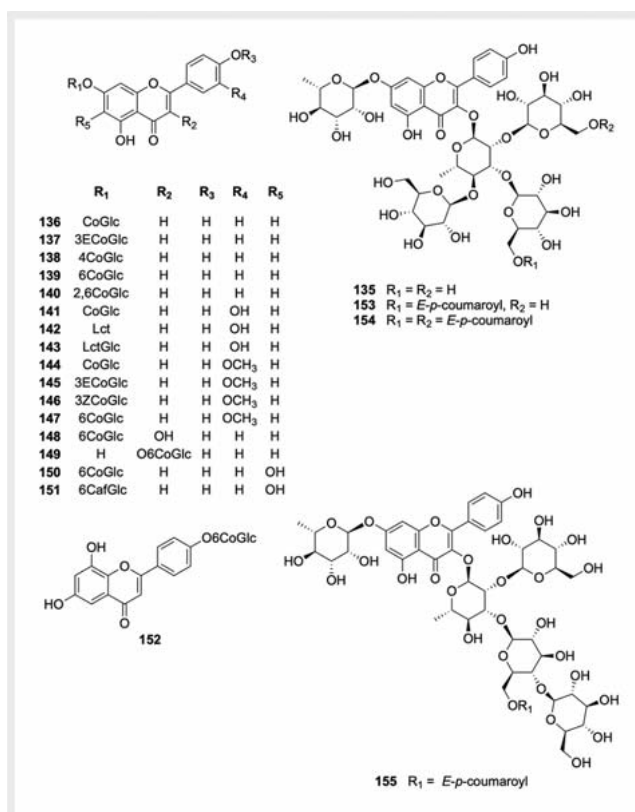
► Fig. 6 Structures of flavonols.

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<sub>3</sub>, 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



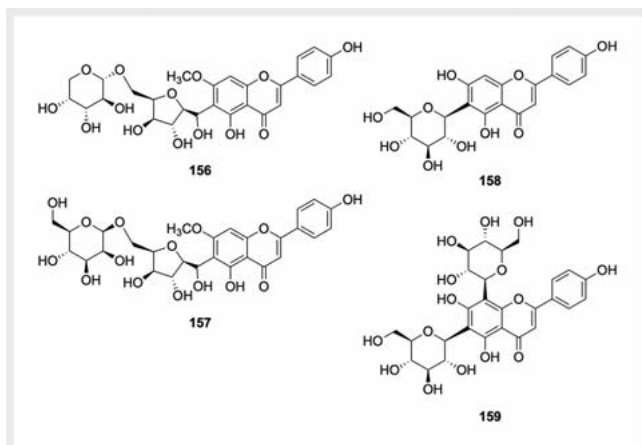
► Fig. 7 Structures of glycosyl flavonoids.



► Fig. 8 Structures of acyl flavonoids.

showing an efficacy comparable to that of indomethacin. Furthermore, the MeOH fraction showed analgesic activity with EC<sub>50</sub> 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).





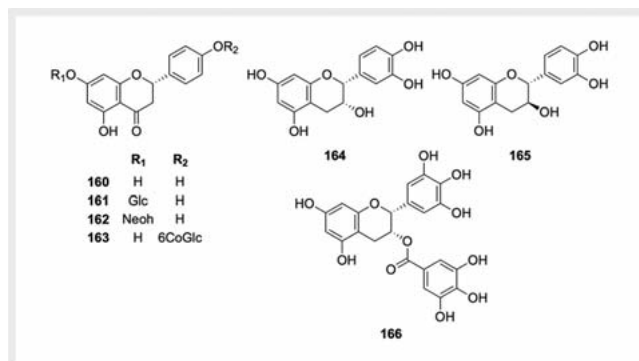
► Fig. 9 Structures of C-glycosyl flavones.

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*- $\beta$ -D-(6''-*E*-*p*-coumaroyl)glucopyranoside (139), apigenin-7-*O*- $\beta$ -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.



► Fig. 10 Structures of flavanones and flavanols.

► 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  $\mu$ g/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 caryophyllene oxide (from 0.07 to 5.20  $\mu$ g/mL) was from 4 to 6 times stronger than that of the whole oil, in which caryophyllene 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 caryophyllene rich EO is in the study of *B. saxatilis* subsp. *brachyodonta* from Turkey [221]. A MIC of 50  $\mu$ g/mL against all of the bacterial genera evaluated was found; caryophyllene, caryophyllene oxide, and *epi*-bicyclosquiphellandrene 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  $\mu$ g/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

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

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

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

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

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

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

continued

► **Table 8** *Continued*

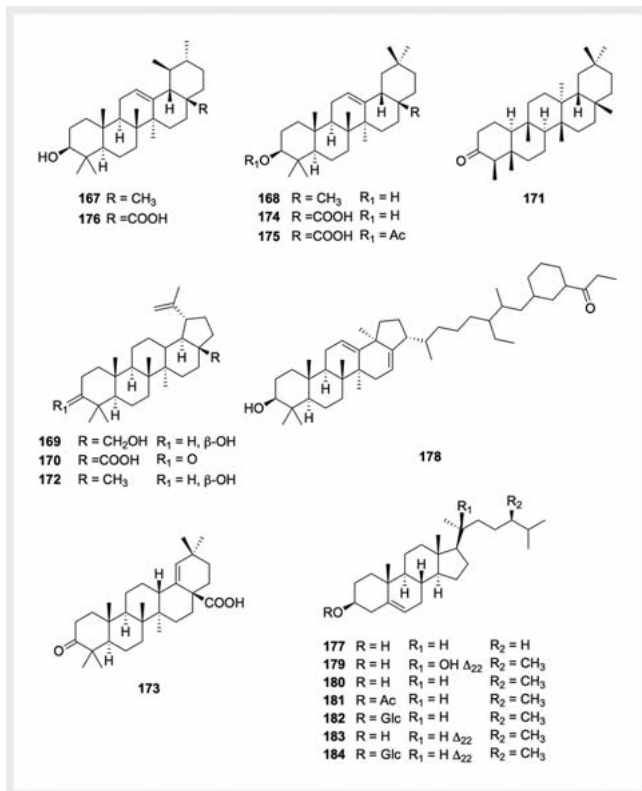
No	Name	Taxa
150	5,6,7,4'-tetrahydroxyflavone-7-O-β-D-(6''-E-p-coumaroyl)glucopyranoside	<i>B. lanata</i> [144]
151	5,6,7,4'-tetrahydroxyflavone-7-O-β-D-(6''-E-caffeoyl)glucopyranoside	<i>B. lanata</i> [144]
152	leufolins B	<i>B. arabica</i> [171]
153	5-hydroxy-2-(4-hydroxyphenyl)-4-oxo-7-[(α-L-rhamnopyranosyl)oxy]-4H-chromen-3-yl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

resveratrol in the extract. Furthermore, in one case, the demonstration of the lack of antibacterial activity versus *Propionibacterium 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<sub>3</sub>, and finally MeOH. The lowest MIC and MBC values were 1.25 mg/mL for the CHCl<sub>3</sub> ext. against *Staphylococcus aureus* and *Enterococcus faecalis*, while the MeOH extc. had a 25 mg/mL MIC for *Listeria monocytogenes* (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.

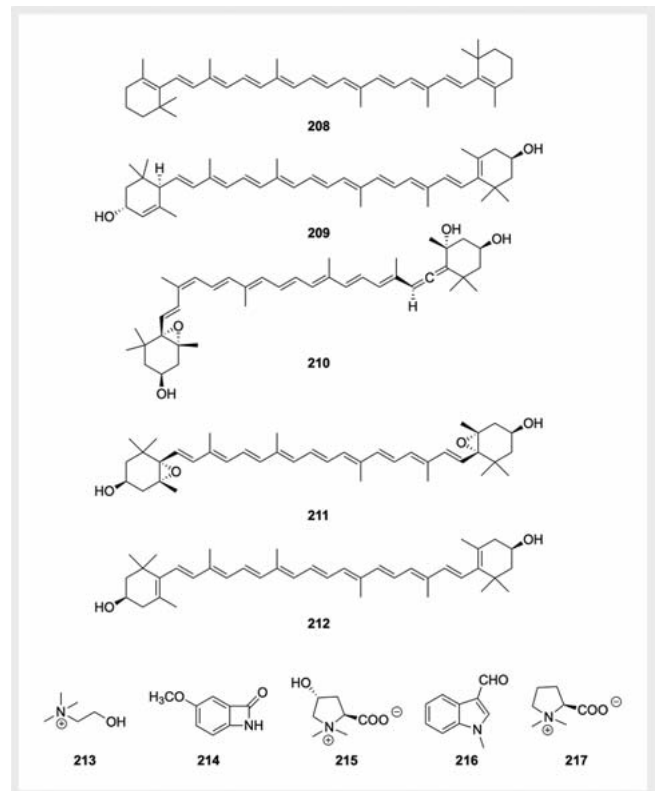
In other cases, the different geographical origin of the plant material may be the cause of strong differences in the bioactivity, as is the case of the EO derived from *O. fruticosa*. The plant har-

vested 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.

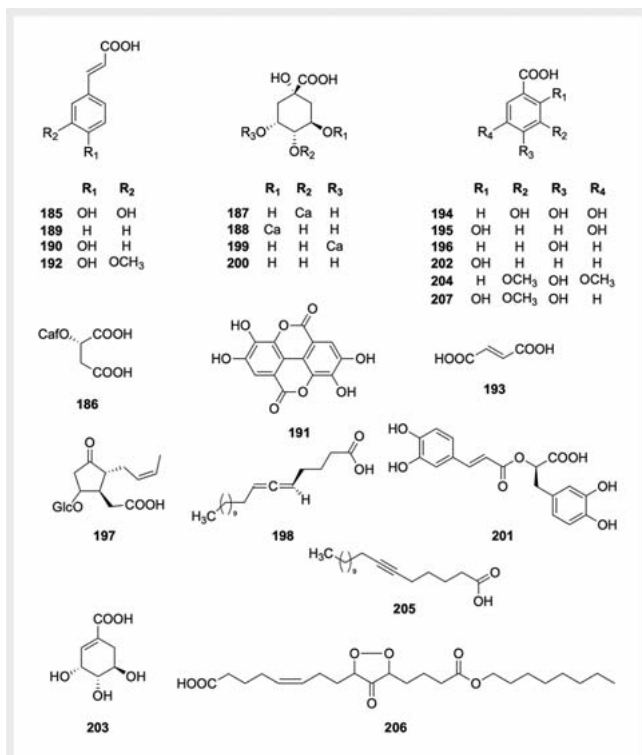
► **Table 14** includes cases where the crude extracts were further portioned with organic solvents in the attempt to concentrate the more active compounds [253, 254, 257], as well as other cases, where the bioactivity was evaluated for single isolated molecules [76, 89, 187]. In most, highly polar extracts 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].



► Fig. 11 Structures of triterpenes and steroids.



► Fig. 13 Structures of carotenoids and nitrogen containing compounds.



► Fig. 12 Structures of carboxylic acids.

## 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<sub>50</sub>: 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. fruticosus* with an IC<sub>50</sub> of 55.1 μg/mL. This taxon was moderately active also against MDA-MB-231 cells with IC<sub>50</sub> 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<sub>50</sub> values (μg/mL): 131.8 for SK-MEL 2, 275.4 for BE (2) C, and 302.0 for U87MG.

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

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

continued

► **Table 9** Continued

No	Names	Taxa
	<b>Carotenoids</b>	
208	carotene	<i>B. lanata</i> [29]
209	lutein	<i>B. lanata</i> [29]
210	neoxanthin	<i>B. lanata</i> [29]
211	violaxanthin	<i>B. lanata</i> [29]
212	zeaxanthin	<i>B. lanata</i> [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].

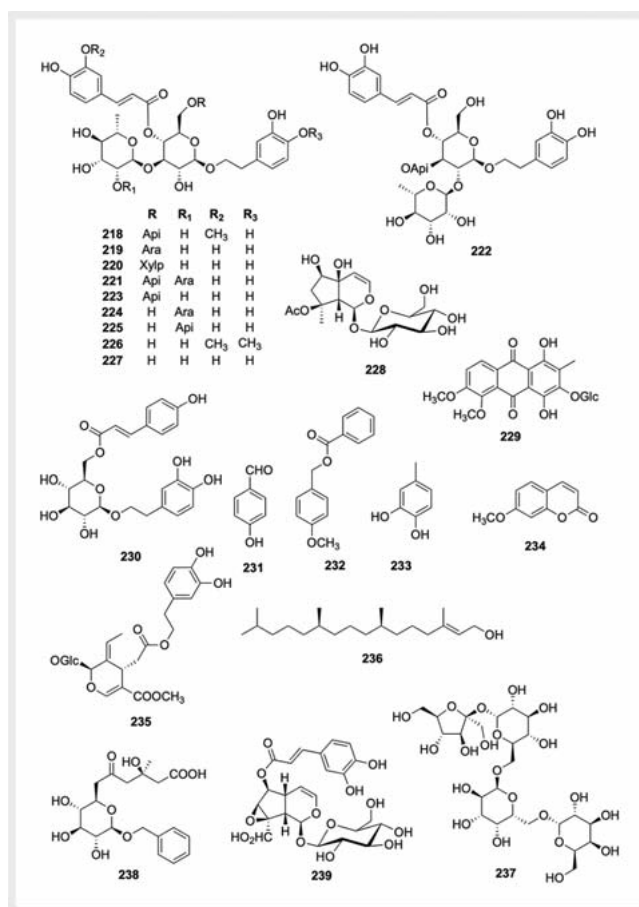
$7\alpha$ -Acetoxyroyleanone (**73**), also occurring in *B. nigra* [115], was shown to be an active anticancer agent against both MIA PaCa-2 and melanoma (MV-3) cancer cell lines ( $IC_{50} = 4.7$  and  $7.4$   $\mu$ g/mL, respectively) [269]. Additionally, it also exhibited cytotoxic activity against 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  $IC_{50} = 0.9$ – $7.6$   $\mu$ g/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  $45$   $\mu$ M 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<sub>2</sub>O 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  $10$   $\mu$ M.



► **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

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

No	Names	Taxa
<b>Nitrogen-containing compounds</b>		
213	choline	<i>B. nigra</i> subsp. <i>foetida</i> [191]
214	cinerealactam E	<i>B. cinerea</i> [88, 182]
215	4-hydroxyprolinebetaine	<i>B. nigra</i> [188], <i>B. undulata</i> [150]
216	1-methylindole-3-carboxaldehyde	<i>B. cinerea</i> [87]
217	stachydrine	<i>B. lanata</i> [138, 192], <i>B. nigra</i> [188], <i>B. nigra</i> subsp. <i>foetida</i> [191], <i>B. undulata</i> [150]
<b>Penylpropanoids</b>		
218	alyssonoside	<i>B. nigra</i> [185, 187]
219	angoroside A	<i>B. nigra</i> [187]
220	arenarioside	<i>B. nigra</i> [94, 187, 193]
221	ballotetroside	<i>B. nigra</i> [94, 185, 187, 194]
222	betonyoside F	<i>B. undulata</i> [150]
223	forsythoside B	<i>B. deserti</i> [89, 90], <i>B. hirsuta</i> [186], <i>B. nigra</i> [94, 115, 185–189, 193], <i>B. pseudodictamnus</i> [162], <i>B. rupestris</i> [186], <i>B. undulata</i> [150]
224	lavandulifolioside	<i>B. nigra</i> [187]
225	lysionotoside	<i>B. undulata</i> [150]
226	martynoside	<i>B. cinerea</i> [88], <i>B. nigra</i> [115]
227	verbascoside (acteoside)	<i>B. deserti</i> [89, 90], <i>B. hirsuta</i> [186], <i>B. lanata</i> [29, 144, 168], <i>B. nigra</i> [94, 185–189, 193, 195], <i>B. pseudodictamnus</i> [162], <i>B. rupestris</i> [186], <i>B. undulata</i> [150]
<b>Other metabolites</b>		
228	8- <i>O</i> -acetylharpagide	<i>O. fruticosa</i> [82]
229	anthroquinone1,4-dihydroxy-6,7-dimethoxy 2-methyl 3- <i>O</i> - $\beta$ -D-glucopyranoside	<i>B. cinerea</i> [165]
230	eutigoside A	<i>B. acetabulosa</i> [161]
231	4-hydroxybenzaldehyde	<i>B. macrodonta</i> [159]
232	4-methoxybenzyl benzoate	<i>B. arabica</i> [184]
233	4-methyl-catechol	<i>B. deserti</i> [157]
234	7-methoxy coumarin	<i>B. lanata</i> [145]
235	oleuropein	<i>B. acetabulosa</i> [135]
236	phytol	<i>B. deserti</i> [24], <i>B. nigra</i> [183], <i>B. nigra</i> subsp. <i>anatolica</i> [196]
237	stachyose	<i>B. nigra</i> subsp. <i>foetida</i> [197]
238	undatuside A	<i>B. cinerea</i> [88]
239	verminoside	<i>B. undulata</i> [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 coxsackie B3 virus with IC<sub>50</sub> values ranging from 100 to 135  $\mu$ g/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*- $\beta$ -neohesperidoside (114), verbascoside (227), apigenin-7-*O*- $\beta$ -D-glucopyranoside (112), and apigenin (76) resulted as margin-

ally 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



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

Taxa	Diterpenes	Flavonoids	Others
<i>B. acetabulosa</i>	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
<i>B. africana</i>	25		
<i>B. andreuzziana</i>	25	83, 86, 116, 121, 127	
<i>B. antalyensis</i>	5, 18		
<i>B. arabica</i>	75	152, 163	176, 179, 180, 182, 185, 192, 194, 196, 206, 232
<i>B. aucheri</i>	4, 5, 10, 27, 28, 29, 30, 31, 34, 44, 46	159	185, 188, 190, 194, 201, 230, 235
<i>B. cinerea</i>	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]
<i>B. cristata</i>	5, 18, 25		204; linoleic acid, oleic acid, palmitic acid, stearic acid, linolenic acid [190]
<i>B. deserti</i>	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
<i>B. glandulosissima</i>		81, 88, 90, 97, 106, 107, 108	
<i>B. hirsuta</i>	25	76, 78, 80, 81, 85, 89, 104, 106, 112, 116, 118, 120, 122, 136, 141, 144, 159	186, 190, 223, 227
<i>B. hispanica</i>	51, 52		
<i>B. inaequidens</i>	5, 25	79, 80, 88, 103, 107–109, 111	
<i>B. lanata</i>	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
<i>B. larendana</i>	5, 18	112, 116, 137, 139	
<i>B. latibracteolata</i>	18	80	
<i>B. macrodonta</i>	18	100, 116, 124, 161, 164–166	185, 187, 188, 190–192, 194–196, 199, 201, 202, 204, 207, 231
<i>B. nigra</i>	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 $\alpha$ -linolenic acid, oleic acid, palmitic acid, stearic acid [198]
<i>B. nigra</i> subsp. <i>anatolica</i>		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]
<i>B. nigra</i> subsp. <i>foetida</i>	5, 9, 10, 37, 47	103, 106, 108, 112, 159	213, 217, 237; palmitic acid, stearic acid, octadecenoic acid, octadecadienoic acid, octadecatrienoic acid [199]
<i>B. nigra</i> f. <i>uncinata</i> .	18		
<i>B. pilosa</i>		76, 139	175, 180, 182–184
<i>B. pseudodictamnus</i>	5, 33, 36	79, 112, 120, 145	186, 223, 227
<i>B. pseudodictamnus</i> subsp. <i>lycia</i>	18, 25		
<i>B. rotundifolia</i>	18, 25	79, 80, 103	
<i>B. rupestris</i>	5, 8, 49		186, 223, 227
<i>B. saxatilis</i>	5, 18, 25, 33	80, 103, 108, 109	
<i>B. saxatilis</i> subsp. <i>brachyodonta</i>	5, 18	80, 105, 108	

continued

► Table 11 Continued

Taxa	Diterpenes	Flavonoids	Others
<i>B. undulata</i>	5, 8, 10, 26	90, 102, 105, 107, 112, 116, 119, 124, 147	183, 215, 217, 222, 223, 225, 227, 239; (-)-carvone, [81]
<i>O. fruticosa</i>	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]
<i>O. integrifolia</i>	43, 48		183; pentatriacontane [100]
<i>O. limbata</i>	6, 7, 53–72	92, 93, 135, 153–155	
<i>O. persica</i>	56, 59, 71, 72	77, 91, 94, 99, 100, 110, 112, 128, 158, 159	168, 177, 180, 181, 183, 185, 189, 196; geraniol, eugenol, ceryl alcohol, hentriacontane [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  $\beta$ -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  $\mu$ L/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*-butanol was active as antitussive by reducing the SO<sub>2</sub>-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 pentylentetrazole, 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 administered 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 administered 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 alloxan-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 administered 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).

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

Taxa		Origin	Main compounds	Ref.
<i>B. andreuzziana</i>	F	G. Akhdar, Libya	caryophyllene (63.1), cis-γ-bisabolene (26.3), selinene (5.0)	[200]
<i>B. aucherii</i>	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]
<i>B. deserti</i>	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]
<i>B. hispanica</i>	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]
<i>B. lanata</i>	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]
<i>B. macedonica</i>	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]
<i>B. nigra</i>	AP	Mazandaran, Iran	caryophyllene oxide (7.9), epi-α-muurolool (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-muurolole (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-vinylguaiacol (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) <sup>a</sup> , 2,2,6-trimethyl-4-methylene-2H-pyran (172) <sup>a</sup> , hexahydrofarnesylacetone (167) <sup>a</sup> , miristic acid (100) <sup>a</sup> , caryophyllene oxide (57) <sup>a</sup> , pentadecanoic acid (50) <sup>a</sup> , palmitoleic acid (40) <sup>a</sup> , germacrene D (40) <sup>a</sup> mg/kg	[211]
	calyx	Kharkov, Ukraine	palmitic acid (1620) <sup>a</sup> , dodecanal (519) <sup>a</sup> , palmitoleic acid (306) <sup>a</sup> , miristic acid (271) <sup>a</sup> , pentadecanoic acid (182) <sup>a</sup> , lauric acid (67) <sup>a</sup> , trans-isoelemicin (67) <sup>a</sup> , hexahydrofarnesylacetone (60) <sup>a</sup> , pentadecene (54) <sup>a</sup> , methyleugenol (40) <sup>a</sup> mg/kg	[211]
	L	Kharkov, Ukraine	palmitic acid (656) <sup>a</sup> , palmitoleic acid (197) <sup>a</sup> , miristic acid (187) <sup>a</sup> , pentadecanoic acid (121) <sup>a</sup> , farnesylacetone (69) <sup>a</sup> , dihydroactinidiolide (44) <sup>a</sup> mg/kg	[211]
S	Kharkov, Ukraine	methylsalicylate (313) <sup>a</sup> , palmitic acid (130) <sup>a</sup> , 2,2,6-trimethyl-4-methylene-2H-pyran (42) <sup>a</sup> , miristic acid (42) <sup>a</sup> mg/kg	[211]	
<i>B. nigra</i> L. subsp. <i>anatolica</i>	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	Çamlıca, 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-dimethyl 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-tert-octyl-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.

► Table 12 Continued

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

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

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

cont.

► Table 13 Continued

Species	Origin	Sample preparation (plant part-solvent)	Test	Ref.
<i>O. persica</i>	Iran	WP: MeOH, then solubilization in <i>n</i> -Hex and CHCl <sub>3</sub>	LPO (% inhib.) 95.87 MeOH, 2.5 <i>n</i> Hex., 1.9 CHCl <sub>3</sub>	[158]
<i>O. persica</i>	Iran	EO	DPPH: IC <sub>50</sub> (mM) 9.76	[228]
<i>O. persica</i>	Iran	EO in flowering EO in fruiting	DPPH: IC <sub>50</sub> (μg/mL) 19.8, 29.2; LPO (% inhib.) 93.8, 63.0	[229]
<i>O. persica</i>	Iran	AP: MeOH	LPO (% inhib.) 95.87	[160]
<i>O. persica</i>	Iran	AP: MeOH, EtOAc	DPPH: IC <sub>50</sub> 0.49 mg/mL for both	[141]
<i>O. persica</i>	Iran	L: 70% EtOH, then partition in PE, EtOAc, CHCl <sub>3</sub> , <i>n</i> -BuOH, MeOH	DPPH: IC <sub>50</sub> (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  $\beta$ -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 fractions of the crude extract, following their solubility in PE, CHCl<sub>3</sub>, 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 and EtOAc extract showed antioxidant activity with IC<sub>50</sub> of 0.49 mg/mL for both. Finally, 4 compounds were isolated from the active extracts: chrysoeriol (91) from EtOAc, 6-methylapigenin (77), api-

genin-7-*O*- $\beta$ -D-glucopyranoside (112), and echinacin (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  $\beta$ -cells was evidenced by histopathological visualization techniques.

The antidiabetic effect of *O. persica* (AP extracted in EtOH/H<sub>2</sub>O 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  $\beta$ -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 were 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.

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

Species	Origin	Sample preparation (plant part: solvent)	Test	Target	Ref
<i>B. acetabukosa</i>	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	<i>S. aureus</i>	[249]
<i>B. acetabukosa</i>	Turkey	L: EtOH	MIC (mg/mL) 32–1024; MBC (µg/mL) 64–1024.	<i>E. faecalis</i> , <i>E. coli</i> , <i>P. mirabilis</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	[250]
<i>B. africana</i>	S. Africa	L: MeOH, W	MIC (µg/mL) 438	<i>K. pneumoniae</i> , <i>A. nauplii</i>	[251]
<i>B. andreuziana</i>	Libya	WP: EtOAc, CHCl <sub>3</sub> , BuOH, W	AD at 50, 100, 150 mg/mL (mm) 7–11	<i>S. aureus</i> , <i>B. subtilis</i> , <i>My phlei</i>	[148]
<i>B. deserti</i>	Algeria	EO L: MeOH	MIC biofilm formation EO (µL/mL) 25–80; MeOH (mg/mL) 3.25–25	<i>S. aureus</i> (ATCC 25923, ATCC 6538-P), <i>S. epidermidis</i> , <i>B. subtilis</i> , <i>B. cereus</i> , <i>S. mutans</i> , <i>M. luteus</i>	[204]
<i>B. deserti</i>	Algeria	AP: CH <sub>2</sub> Cl <sub>2</sub> , MeOH; then isolat. compds: 40, 223, 227	MIC (µM): 46–162	<i>E. faecalis</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	[90]
<i>B. inaequidens</i>	Turkey	AP: Ac; isolat. compds: 5, 25, 79, 103, 105, 107, 108, 109	MIC (µg/mL): 25–50	<i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	[76]
<i>B. nigra</i>	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	<i>S. aureus</i>	[252]
<i>B. nigra</i>	Pakistan	S, L, R: EtOH then part. between W and <i>n</i> -Hex, EtOAc, CHCl <sub>3</sub> , BuOH	AD at 5 mg/mL (mm) 8–30	<i>E. coli</i> , <i>S. aureus</i> , <i>P. mirabilis</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>S. typhi</i>	[253]
<i>B. nigra</i>	Serbia	S, L: EO	MIC (µg/mL): 2.5–5	<i>E. coli</i> , <i>S. aureus</i> , <i>B. mycoides</i> , <i>M. lysodeikticus</i> , <i>B. subtilis</i> , <i>K. pneumoniae</i> , <i>C. albicans</i>	[209]
<i>B. nigra</i>	France	shoots: 50% EtOH then isolat. compds: 220, 223, 227	MIC (µg/mL): 64–128	<i>S. aureus</i> , <i>S. aureus</i> MRSA, <i>P. mirabilis</i>	[187]
<i>B. nigra</i>	Italy	WP: W	MIC, dose-dependent biofilm formation inhibition, max inhib. at 128 µg/mL	<i>S. aureus</i> MRSA	[254]
<i>B. nigra</i> spp. <i>anatolica</i>	Turkey	L: EtOH	MIC (µg/mL) 250–1000	<i>B. subtilis</i> , <i>B. cereus</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. vulgaris</i> , <i>S. typhimurium</i> , <i>P. aeruginosa</i>	[255]
<i>B. nigra</i> spp. <i>anatolica</i>	Turkey	L: EtOH	AD at 50 µg/mL (mm) 10.0–19.2	<i>B. cereus</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>S. capitis</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>P. acnes</i> , <i>M. nonliquefaciens</i> ,	[256]
<i>B. nigra</i> ssp. <i>foetida</i>	Italy	EO	MIC, MBC (mg/mL): 3–7	<i>E. coli</i> , <i>E. cloacae</i> , <i>P. aeruginosa</i> , <i>F. fluorescens</i> , <i>S. aureus</i> , <i>S. epidermidis</i>	[216]
<i>B. pseudo-dictamnus</i>	Pakistan	S, L, R: EtOH then part. bet. W/ <i>n</i> -Hex, EtOAc, CHCl <sub>3</sub> , BuOH	AD at 2 µg/mL (mm) 0.8–20	<i>E. coli</i> , <i>S. aureus</i> , <i>P. mirabilis</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>S. typhi</i>	[257]
<i>B. pseudo-dictamnus</i>	Greece	EO	MIC (mg/mL) 0.45–10.15, > 20 for <i>E. coli</i>	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i> , <i>E. cloacae</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	[220]
<i>B. rotundifolia</i>	Turkey	WP: MeOH then the extract was split in W-soluble and W-insoluble fractions	MIC (µg/mL): > 72	<i>S. pneumoniae</i> , <i>B. cereus</i> , <i>A. lwoffii</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>C. perfringens</i>	[238]
<i>B. saxatilis</i>	Turkey	F: Ac: then isolat. compds: 5, 18, 25	MIC (µg/mL): 25–50	<i>S. aureus</i> , <i>S. faecalis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> .	[80]
<i>B. saxatilis</i> ssp. <i>brachyodonta</i>	Turkey	EO	MIC (µg/mL): 25–50	<i>E. coli</i> , <i>E. faecalis</i> , <i>B. subtilis</i> , <i>S. typhimurium</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>K. pneumoniae</i>	[221]
<i>O. fruticosa</i>	Egypt	EO	MIC (µg/mL): 1.5–6	<i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>S. epidermidis</i> , <i>S. faecalis</i> , <i>K. aerogenes</i>	[224]
<i>O. fruticosa</i> ssp. <i>schimperi</i>	Yemen	EO	MIC (µg/mL): 310–1250	<i>B. cereus</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	[222]
<i>O. integrifolia</i>	Ethiopia	L: 80% MeOH, CHCl <sub>3</sub>	MIC (mg/mL): 0.312	<i>M. tuberculosis</i>	[258]

cont.

► Table 14 Continued

Species	Origin	Sample preparation (plant part: solvent)	Test	Target	Ref
<i>O. integrifolia</i>	Ethiopia	EO	MIC (mg/mL) 5–100	<i>E. coli</i> 18/9, <i>E. coli</i> ATCC 10536, <i>E. coli</i> CD/99/1, <i>E. coli</i> K88, <i>E. coli</i> RP4, <i>E. coli</i> VC Sonawave 3 : 37 C, <i>P. aeruginosa</i> , <i>S. boydii</i> , <i>S. dysentery</i> , <i>S. flexneri</i> , <i>S. soneii</i> 1, <i>S. soneii</i> BCH 217, <i>V. cholera</i> , <i>B. subtilis</i>	[56]
<i>O. limbata</i>	Pakistan	WP: 70% EtOH. then ext. solubilized in DMSO, EtOH, MeOH	MIC (mg/mL): 0.2–5	<i>B. subtilis</i> , <i>L. monocytogenes</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>Salmonella</i> spp.	[259]
<i>O. persica</i>	Iran	AP: MeOH	MIC (mg/mL): 0.5–2	<i>E. coli</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>K. pneumonia</i> , <i>A. niger</i>	[260]
<i>O. persica</i>	Iran	AP: 70% EtOH, <i>n</i> -Hex, CHCl <sub>3</sub> , MeOH	MIC (mg/mL): 1.25–25	<i>E. coli</i> , <i>L. monocytogenes</i> , <i>E. faecalis</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>B. subtilis</i> , <i>P. aeruginosa</i> , <i>Salmonella</i> spp., <i>Klebsiella</i> 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 $\beta$ -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<sub>2</sub>O<sub>2</sub> and FRAP values increased by dexamethasone were also normalized in the animals receiving the plant brew.



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

Species	Origin	Sample preparation (plant part: solvent)	Test	Target	Ref.
<i>B. acetabulosa</i>	Turkey	L, R: 50% EtOH	MIC (mg/mL) 1.56–25.0	<i>C. albicans</i> , <i>C. tropicalis</i> , <i>C. guilliermondii</i> , <i>Cryptococcus neoformans</i> , <i>C. laurentii</i>	[263]
<i>B. deserti</i>	Algeria	EO L: MeOH	MIC biofilm formation EO (μL/mL) 25; MeOH extr. (mg/mL) 12.5	<i>C. albicans</i>	[204]
<i>B. inaequidens</i>	Turkey	AP: Ac; then isolat. compds: 5, 25, 79, 103, 105, 107, 108, 109	MIC (μg/mL) 3.1–12.5	<i>C. albicans</i> , <i>C. crusei</i>	[76]
<i>B. nigra</i>	Paikstan	S, L, R: EtOH then partition between W/n-Hex, EtOAc, CHCl <sub>3</sub> , BuOH	Agar tube dilution, results reported as inhibition “positive” or “negative”; crude extrat always positive at 2 mg/mL	<i>A. niger</i> , <i>A. flavus</i> , <i>A. fumigatus</i> , <i>F. solani</i>	[253]
<i>B. nigra</i> ssp. <i>anatolica</i>	Turkey	L: EtOH	MIC (μg/mL): 500–1000	<i>C. albicans</i> , <i>D. hansenii</i> , <i>K. fragilis</i> , <i>R. rubra</i>	[255]
<i>B. nigra</i> ssp. <i>foetida</i>	Italy	EO	MIC (mg/mL) 5.5; MBC (mg/mL) 15.0	<i>C. albicans</i> , <i>C. glabrata</i> , <i>C. tropicalis</i>	[216]
<i>B. pseudodictamnus</i>	Pakistan	S, L, R: EtOH then partition between W/n-Hex, EtOAc, CHCl <sub>3</sub> , BuOH	Agar tube dilution, results reported as inhibition “positive” or “negative” at 2 mg/mL	<i>A. niger</i> ; <i>A. fumigates</i> , <i>A. flavus</i> ; <i>F. solani</i>	[257]
<i>B. pseudodictamnus</i>	Greece	EO	Not active	<i>C. albicans</i> , <i>C. tropicalis</i> , <i>C. glabrata</i>	[220]
<i>B. rotundifolia</i>	Turkey	WP: MeOH then the extract was split in W-soluble and W-insoluble fractions	MIC (μg/mL) > 72	<i>C. albicans</i> , <i>C. krusei</i>	[238]
<i>B. saxatilis</i>	Turkey	L: Ac then isolat. compds: 5, 18, 25	Agar diluiton MIC (μg/mL): 1.5–3.1	<i>C. albicans</i>	[80]
<i>B. saxatilis</i> ssp. <i>brachyodonta</i>	Turkey	EO	MIC (μg/mL): 25	<i>C. albicans</i> (clinic strain), <i>C. parapsilosis</i>	[221]
<i>B. undulata</i>	Egypt	L, S, F: EtOH, EtOAc, CHCl <sub>3</sub> , n-Hex	MIC (mg/mL): 25 – > 150	<i>T. rubrum</i> , <i>T. tonsurans</i> , <i>C. albicans</i> , <i>C. tropicalis</i> , <i>P. lilacinus</i> , <i>P. variotii</i> , <i>S. berricaultii</i>	[264]
<i>O. integrifolia</i>	Ethiopia	EO	MIC (μg/mL): 50–100	<i>A. niger</i> , <i>C. albicans</i> , <i>P. funiculosum</i> , <i>P. notatum</i>	[56]
<i>O. fruticosa</i>	Egypt	EO	MIC (μg/mL): 6.0, 16.0	<i>C. albicans</i> , <i>S. cerevisiae</i>	[224]
<i>O. limbata</i>	Paikstan	WP: MeOH, then partition in n-Hex, CHCl <sub>3</sub> , EtOAc, BuOH	MIC (mg/mL) 0.18–1.5	<i>S. setubal</i> , <i>P. pickettii</i> , <i>S. aureus</i> , <i>M. luteus</i>	[265]
<i>O. persica</i>	Iran	AP: MeOH	MIC (mg/mL): 1.0	<i>C. albicans</i>	[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<sub>2</sub>O 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 appear-

ing in the literature in the same year [101] resulted in the bio-guided 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<sub>50</sub> 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<sub>50</sub> of CQ with 30% of extract caused a 26% increase in the mean effective dose.

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<sub>50</sub> 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<sub>4</sub> 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<sub>4</sub>-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<sub>2</sub>O 1:1 in a CCl<sub>4</sub> 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<sub>50</sub> 22.3, 17.5 and 14.2 µM, respectively) than for the former (IC<sub>50</sub> 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-methoxy-patagonic acid (71), patagonic acid (72), and limbatenolides A–C (54–56). All of the compounds showed inhibitory activity with BChE with IC<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> = 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 3β-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<sub>3</sub>, *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<sub>50</sub> values 1.6 and 3.6 µM, respectively) when compared to serine, used as a positive control (IC<sub>50</sub> 0.93 µM). On the other hand, very weak activity was observed against acetylcholinesterase (IC<sub>50</sub> values 74.5 and 72.3 µM, respectively), compared to eserine (IC<sub>50</sub> = 0.04 µM) [171]. The new steroid leucisterol (179), also isolated from the same species, showed potent inhibitory activity against butyrylcholinesterase enzyme (IC<sub>50</sub> = 3.2 µM). [181].

## 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  $^{13}\text{C}$  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 anti-diabetic.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

- [1] Erdtman G. Pollen morphology and plant taxonomy. IV. Labiatae, Verbenaceae and Avicennaceae. *Svensk Bot Tidskr* 1945; 39: 279–285
- [2] Cantino PD, Sanders RW. Subfamilial classification of Labiatae. *Syst Bot* 1986; 11: 163–185
- [3] Patzák A. Revision der Gattung *Ballota* Section *Ācanthoprasium* und Section *Beringeria*. *Ann Naturhist Mus Wien* 1958; 62: 57–86
- [4] Patzák A. Revision der Gattung *Ballota* Section *Ācanthoprasium* und Section *Beringeria*. *Ann Naturhist Mus Wien* 1959; 63: 33–81
- [5] Patzák A. Revision der Gattung *Ballota* Section *Ācanthoprasium* und Section *Beringeria*. *Ann Naturhist Mus Wien* 1961; 64: 42–56
- [6] The Plant List. Available at [www.theplantlist.org](http://www.theplantlist.org). Accessed September 5, 2018
- [7] Bendiksby M, Thorbek L, Scheen AC, Lindqvist C, Ryding O. An updated phylogeny and classification of Lamiaceae subfamily Lamioideae. *Taxon* 2011; 60: 471–484
- [8] Harley RM, Atkins S, Budantsev AL, Cantino PD, Conn BJ, Grayer R, Harley MM, De Kok R, Krestovskaja T, Morales R, Paton AJ, Ryding O, Upson T. Labiatae. In: Kadereit JW, ed. *The Families and Genera of vascular Plants*. Vol. 7: Lamiales. Berlin, Heidelberg: Springer; 2004: 167–275
- [9] Hedge IC. A global Survey of the Biogeography of the Labiatae. In: Harley RM, Reynolds T, eds. *Advances in labiate Science*. Kew: The Royal Botanic Gardens; 1992: 7–17
- [10] Scheen AC, Albert VA. Nomenclatural and taxonomic changes within the *Leucas* clade (Lamioideae; Lamiaceae). *Syst Geogr Pl* 2007; 77: 229–238
- [11] Tuzlaci E, Sadikoğlu E. Turkish folk medicinal plants, part VI: Koçarlı (Aydin). *J Fac Pharm Istanbul* 2007; 39: 25–37
- [12] Dumlu MU, Bulut GE. Some biological activity investigations on *Ballota acetabulosa*. *J Fac Pharm Istanbul* 2007; 39: 53–56
- [13] Nortje JM, Van Wyk BE. Medicinal plants of the Kamiesberg, Namaqualand, South Africa. *J Ethnopharmacol* 2015; 171: 205–222
- [14] Scott G, Springfield EP, Coldrey N. A pharmacognostical study of 26 South African plant species used as traditional medicines. *Pharm Biol* 2004; 42: 186–213
- [15] Cock IE, van Vuuren SF. Anti-proteus activity of some South African medicinal plants: their potential for the prevention of rheumatoid arthritis. *Inflammopharmacology* 2014; 22: 23–36
- [16] Akhtar K, Khan SB, Malik A. Phytochemistry and pharmacological aspects of *Leucas urticifolia* (Vahl) Benth. *J Pharm Res Health Care* 2010; 2: 197–203
- [17] Sadeghi Z, Kuehstani K, Abdollahi V, Mahmood A. Ethnopharmacological studies of indigenous medicinal plants of Saravan region, Baluchistan, Iran. *J Ethnopharmacol* 2014; 153: 111–118
- [18] Bano A, Ahmad M, Zafar M, Sultana S, Rashid S, Khan MA. Ethnomedicinal knowledge of the most commonly used plants from Deosai Plateau, Western Himalayas, Gilgit Baltistan, Pakistan. *J Ethnopharmacol* 2014; 155: 1046–1052
- [19] Natarajan B, Paulsen BS, Korneliussen V. An ethnopharmacological study from Kulu district, Himachal Pradesh, India: traditional knowledge compared with modern biological science. *Pharm Biol* 2000; 38: 129–138
- [20] Rawat R, Vashistha DP. *Roylea cinerea* (D. Don) Baillon: a traditional curative of diabetes, its cultivation prospects in Srinagar Valley of Uttarakhand. *Int J Adv Pharm Biol Chem* 2013; 2: 372–375
- [21] Dangwal LR. Ethnomedicinal plants used for the treatment of diabetes among the villagers of Narendra Nagar block, district Tehri Garhwal, Uttarakhand, India. *World J Pharm Pharm Sci* 2015; 4: 1178–1184
- [22] Bisht S, Pangti J, Pundir S, Das A, Devi J. Total phenolic and total flavonoid compounds in the leaves of *Roylea cinerea* using hydroalcoholic extract. *World J Pharm Pharm Sci* 2016; 7: 1753–1759
- [23] Hammiche V, Maiza K. Traditional medicine in Central Sahara: pharmacopoeia of Tassili N'ajjer. *J Ethnopharmacol* 2006; 105: 358–367
- [24] Dendougui H, Seghir S, Belloum Z, Benayache F, Leon F, Brouard I, Bermejo J, Benayache S. A new labdane diterpene and other constituents from *Marrubium deserti* Noe ex Coss. *Rec Nat Prod* 2011; 5: 300–304
- [25] Edziri H, Mastouri M, Aouni M, Verschaeve L. Polyphenols content, antioxidant and antiviral activities of leaf extracts of *Marrubium deserti* growing in Tunisia. *S Afr J Bot* 2012; 80: 104–109
- [26] Teixidor-Toneu I, Martin GJ, Ouhammou A, Puri RK, Hawkins JA. An ethnomedicinal survey of a Tashelhit-speaking community in the High Atlas, Morocco. *J Ethnopharmacol* 2016; 188: 96–110
- [27] Kechar K, Hellal B, Ayad N, Benahmed-Djilali A. Ethnobotanical investigation of *Ballota hirsuta* (Benth) at Sidi Bel Abbes (Algeria). *Phytotherapie* 2016; 14: 343–348
- [28] Zheng YF, Yin W, Lin LL, Du SS, Shan T, Wang Y. Advances in studies on *Panzeria alaschanica*. *Zhong Cao Yao* 2007; 38: 1434–1436
- [29] Olennikov DN, Tankhaeva LM. Chemical study of *Panzerina lanata*. *Chem Nat Compd* 2011; 47: 802–804
- [30] Rexhepi B, Mustafa B, Hajdari A, Rushidi-Rexhepi J, Quave CL, Pieroni A. Traditional medicinal plant knowledge among Albanians, Macedonians and Gorani in the Sharr Mountains (Republic of Macedonia). *Genet Resour Crop Evol* 2014; 60: 2055–2080
- [31] Ciocarlan N. Family *Lamiaceae*: main important spontaneous medicinal and aromatic species in the Republic of Moldova. *J Bot* 2016; 8: 86–91
- [32] Šarić-Kundalić B, Dobeš C, Klatter-Asselmeyer V, Saukel J. Ethnobotanical survey of traditionally used plants in human therapy of east, north and north-east Bosnia and Herzegovina. *J Ethnopharmacol* 2011; 133: 1051–1076
- [33] Pieroni A. Medicinal plants and food medicines in the folk traditions of the upper Lucca Province, Italy. *J Ethnopharmacol* 2000; 70: 235–273
- [34] Mulas M. Traditional uses of Labiatae in the Mediterranean area. *Acta Hort* 2006; 723: 25–32
- [35] Pieroni A, Quave C, Nebel S, Heinrich M. Ethnopharmacy of the ethnic Albanians (Arbëreshë) of northern Basilicata, Italy. *Fitoterapia* 2001; 73: 217–241
- [36] Pieroni A, Quave CL, Santoro RF. Folk pharmaceutical knowledge in the territory of the Dolomiti Lucane, inland southern Italy. *J Ethnopharmacol* 2004; 95: 373–384

- [37] Redžić SS. The ecological aspect of ethnobotany and ethnopharmacology of population in Bosnia and Herzegovina. *Coll Antropol* 2007; 31: 869–890
- [38] Nićiforović N, Mihailović V, Mašković P, Solujić S, Stojković A, Muratspahić DP. Antioxidant activity of selected plant species; potential new sources of natural antioxidants. *Food Chem Toxicol* 2010; 48: 3125–3130
- [39] Gonzalez JA, Garcia-Barriuso M, Gordaliza M, Amich F. Traditional plant-based remedies to control insect vectors of disease in the Arribes del Duero (Western Spain): an ethnobotanical study. *J Ethnopharmacol* 2011; 138: 595–601
- [40] Yeflilada E, Honda G, Sezik E, Tabata M, Goto T, Ikeshiro Y. Traditional medicine in Turkey IV. Folk medicine in the Mediterranean subdivision. *J Ethnopharmacol* 1993; 39: 31–38
- [41] Yeflilada E, Honda G, Sezik E, Tabata M, Fujita T, Tanaka T, Takeda Y, Takaishi Y. Traditional medicine in Turkey V. Folk medicine in the inner Taurus Mountains. *J Ethnopharmacol* 1995; 46: 133–152
- [42] Tuzlaci E, Aymaz PE. Turkish folk medicinal plants, part IV: Gönen (Balıkesir). *Fitoterapia* 2001; 72: 323–343
- [43] Kültür S. Medicinal plants used in Kirklareli Province (Turkey). *J Ethnopharmacol* 2007; 111: 341–364
- [44] Mothana RAA, Kriegisch S, Harms M, Wende K, Lindequist U. Assessment of selected Yemeni medicinal plants for their *in vitro* antimicrobial, anticancer, and antioxidant activities. *Pharm Biol* 2011; 49: 200–210
- [45] Mothana RA, Al-Musayeb NM, Al-Ajmi MF, Cos P, Maes L. Evaluation of the *in vitro* antiparasitic, antileishmanial, and antitrypanosomal activity of medicinal plants used in Saudi and Yemeni traditional medicine. *Evid Based Complement Alternat Med* 2014; 2014: 905639: 1–7
- [46] Meragiaw M, Asfaw Z, Argaw M. The status of ethnobotanical knowledge of medicinal plants and the impacts of resettlement in Delanta, Northwestern Wello, Northern Ethiopia. *Evid Based Complement Alternat Med* 2016; 2016: 5060247
- [47] Kidane D, Tomass Z, Dejene T. Community knowledge of traditional mosquito repellent plants in Kolla Temben District, Tigray, Northern Ethiopia. *Sci Res Essays* 2013; 8: 1139–1144
- [48] Seyoum G, Zerihun G. An ethnobotanical study of medicinal plants in Debre Libanos Wereda, Central Ethiopia. *Afr J Plant Sci* 2014; 8: 366–379
- [49] Rahman MA, Mossa JS, Al-Said MS, Al-Yahya MA. Medicinal plant diversity in the flora of Saudi Arabia 1: a report on seven plant families. *Fitoterapia* 2004; 75: 149–161
- [50] Waka M, Hopkins RJ, Curtis C. Ethnobotanical survey and testing of plants traditionally used against hematophagous insects in Eritrea. *J Ethnopharmacol* 2004; 95: 95–101
- [51] Teklehaymanot T, Giday M, Medhin G, Mekonnen Y. Knowledge and use of medicinal plants by people around Debre Libanos monastery in Ethiopia. *J Ethnopharmacol* 2007; 111: 271–283
- [52] Karunamoorthi K, Husen E. Knowledge and self-reported practice of the local inhabitants on traditional insect repellent plants in Western Hararghe zone, Ethiopia. *J Ethnopharmacol* 2012; 141: 212–219
- [53] Giday G, Teklehaymanot T, Animut A, Mekonnen Y. Medicinal plants of the Shinasha, Agew-awi and Amhara peoples in northwest Ethiopia. *J Ethnopharmacol* 2007; 110: 516–525
- [54] Mekuria AB, Belachew SA, Tegegn HG, Ali DS, Netere AK, Lemlemu E, Erku DA. Prevalence and correlates of herbal medicine use among type 2 diabetic patients in Teaching Hospital in Ethiopia: a cross-sectional study. *BMC Complement Alternat Med* 2018; 18: 85
- [55] Tesfaye H, Hishe M, Badasa S. Phytochemical and ethno botanical study of medicinal plants used to treat ectoparasites in ruminant animals in eastern Tigray, northern Ethiopia. *Int J Pharmacogn (Panchkula, India)* 2015; 2: 466–472
- [56] Tadesse S, Messele B, Seyoum A, Mazumder A, Bucar F, Asres K. Essential oil of *Otostegia integrifolia* Benth: composition, antimicrobial and antioxidant activities. *Ethiop Pharm J* 2011; 29: 79–86
- [57] Chopra RN, Nayar SL, Chopra IC. Glossary of Indian medicinal Plant. India: Indian Council of Scientific & Industrial Research; 1956: 183
- [58] Adnan M, Hussain J, Shah MT, Shinwari ZK, Ullah F, Bahader A, Khan N, Khan AL, Watanabe T. Proximate and nutrient composition of medicinal plants of humid and sub-humid regions in north-west Pakistan. *J Med Plants Res* 2010; 4: 339–345
- [59] Abbasi AM, Khan MA, Ahmad M, Zafar M, Jahan S, Sultana S. Ethnopharmacological application of medicinal plants to cure skin diseases and in folk cosmetics among the tribal communities of North-West Frontier Province, Pakistan. *J Ethnopharmacol* 2010; 128: 322–335
- [60] Haq F, Ahmad H, Alam M. Traditional uses of medicinal plants of Nandiar Khuwarr catchment (District Battagram), Pakistan. *J Med Plants Res* 2011; 5: 39–48
- [61] Rehman K, Mashwani ZUR, Khan MA, Ullah Z, Chaudhary HJ. An ethno botanical perspective of traditional medicinal plants from the Khattak tribe of Chonhtra Karak, Pakistan. *J Ethnopharmacol* 2015; 165: 251–259
- [62] Murad W, Ahmad A, Gilani SA, Khan MA. Indigenous knowledge and folk use of medicinal plants by the tribal communities of Hazar Nao forest, Malakand district, North Pakistan. *J Med Plants Res* 2011; 5: 1072–1086
- [63] Iqbal H, Sher Z, Khan ZU. Medicinal plants from salt range Pind Dadan Khan, district Jhelum, Punjab, Pakistan. *J Med Plants Res* 2011; 5: 2157–2168
- [64] Adnan M, Bibi R, Azizullah A, Andaleeb R, Mussarat S, Tariq A, Ullah R, Elsalam NM, Khan AL, Begum S. Ethnomedicinal plants used against common digestive problems. *Afr J Tradit Complement Altern Med* 2015; 12: 99–117
- [65] Rashid S, Ahmad M, Zafar M, Sultana S, Ayub M, Khan MA, Yaseen G. Ethnobotanical survey of medicinally important shrubs and trees of Himalayan region of Azad Jammu and Kashmir, Pakistan. *J Ethnopharmacol* 2015; 166: 340–351
- [66] Ahmad L, Semotiuk A, Zafar M, Ahmad M, Sultana S, Liu QR, Zada MP, Abidin SZU, Yaseen G. Ethnopharmacological documentation of medicinal plants used for hypertension among the local communities of DIR Lower, Pakistan. *J Ethnopharmacol* 2015; 175: 138–146
- [67] Hussain S, Murtaza G, Mehmood A, Qureshi RA. Conservation of indigenous knowledge of medicinal plants of Western Himalayan region Rawalakot, Azad Kashmir, Pakistan. *Pak J Pharm Sci* 2017; 30: 773–782
- [68] Bibi R, Tariq A, Mussarat S, Khan SN, Rahman H, Allah EFA, Ullah R, Adnan M. Ethnomedicinal, phytochemical and antibacterial activities of medicinal flora of Pakistan used against *Pseudomonas aeruginosa* – a review. *Pak J Pharm Sci* 2017; 30: 2285–2300
- [69] Habiba U, Ahmad M, Shinwari S, Sultana S, Shinwari ZK, Zafar M. Antibacterial and antifungal potential of Himalayan medicinal plants for treating wound infections. *Pak J Bot* 2016; 48: 371–375
- [70] Savona G, Piozzi F, Hanson JR, Siverns M. Structures of three new diterpenoids from *Ballota* species. *J Chem Soc Perkin I* 1977: 322–324
- [71] Rustaiyan A, Mosslemin-Kupaii MH, Zdero C. Furoolabdanes and related compounds from *Ballota aucheri*. *Phytochemistry* 1992; 31: 344–346
- [72] Yilmaz BS, Çitoğlu GS. High performance liquid chromatographic analysis of some diterpenoids of the *Ballota* species. *FABAD J Pharm Sci* 2003; 28: 13–17
- [73] Çitoğlu GS, Yilmaz BS, Tarikahya B, Tipirdamaz R. Chemotaxonomy of *Ballota* species. *Chem Nat Compd* 2005; 41: 299–302
- [74] Rustaiyan A, Mosslemin-Kupaii MH, Papastergiou F, Jakupovic J. Persiane, a dimeric diterpene from *Ballota aucheri*. *Phytochemistry* 1995; 40: 875–879
- [75] Yilmaz BS, Çitoğlu GS. Chemical constituents of *Ballota* L. species. *Ankara Üniversitesi Eczacılık Fakültesi Dergisi* 2003; 32: 37–53
- [76] Çitoğlu GS, Sever B, Antus S, Baitz-Gács E, Altanlar N. Antifungal diterpenoids and flavonoids from *Ballota inaequidens*. *Pharm Biol* 2004; 42: 659–663

- [77] Savona G, Piozzi F, Hanson JR. 13-Hydroxyballonigrinolide, a new diterpenoid from *Ballota lanata*. *Phytochemistry* 1978; 17: 2132–2133
- [78] Savona G, Piozzi F, Hanson JR, Siverns M. New diterpenoids from species of genus *Ballota*. *Chim Ind* 1976; 58: 378
- [79] Savona G, Bruno M, Piozzi F, Barbagallo C. Diterpenes from *Ballota* species. *Phytochemistry* 1982; 21: 2132–2133
- [80] Çitoğlu G, Tanker M, Sever B, Englert J, Anton R, Altanlar N. Antibacterial activities of diterpenoids isolated from *Ballota saxatilis* subsp. *saxatilis*. *Planta Med* 1998; 40: 484–485
- [81] Hussein AA, Jimeno ML, Rodríguez B. Structural and spectral assignment of a new diterpenoid isolated from *Ballota undulata* and complete H and C NMR data assignment for three other structurally related compounds. *Mag Res Chem* 2007; 45: 899–901
- [82] Al-Musayeib NM, Abbas FA, Ahmad MS, Mossa JS, El-Ferally FS. Labdane diterpenes from *Otostegia fruticosa*. *Phytochemistry* 2000; 54: 771–775
- [83] Farooq U, Khan A, Khan AF, Khan SS, Sarwar R, Ahmad VU, Waseem A. Two new ballonigrin-type diterpenoids from the roots of *Ballota limbata*. *Nat Prod Commun* 2012; 7: 149–150
- [84] Savona G, Piozzi F, Hanson JR, Siverns M. The structure of ballotenol, a new diterpenoid from *Ballota nigra*. *J Chem Soc Perkin I* 1977: 497–499
- [85] Savona G, Piozzi F, Hanson JR, Siverns M. Structure of ballotinone, a diterpenoid from *Ballota nigra*. *J Chem Soc Perkin I* 1976: 1607–1609
- [86] Prakash O, Bhakuni DS, Kapil RS, Rao GSRS, Ravindranath B. Diterpenoids of *Roylea calycina* (Roxb.) Briq. *J Chem Soc Perkin I* 1979: 1305–1308
- [87] Sharma R, Chebolu R, Ravikumar PC. Isolation and structural elucidation of two new labdane diterpenoids from the aerial part of *Roylea cinerea*. *Phytochemistry Lett* 2015; 13: 187–193
- [88] Sharma R, Mohammadi-Ostad-Kalayeh S, Stahl F, Zeilinger C, Dräger G, Kirschning A, Ravikumar PC. Two new labdane diterpenoids and one new – lactam from the aerial parts of *Roylea cinerea*. *Phytochemistry Lett* 2017; 19: 101–107
- [89] Zaabat N, Hay AE, Michalet S, Darbour N, Bayet C, Skandrani I, Chekir-Ghedira L, Akkal S, Dijoux-Franca MG. Antioxidant and antigenotoxic properties of compounds isolated from *Marrubium deserti* de Noé. *Food Chem Toxicol* 2011; 49: 3328–3335
- [90] Zaabat N, Darbour N, Bayet C, Michalet S, Doléans-Jordheim A, Chekir-Ghedira L, Akkal S, Dijoux-Franca MG. Preliminary study of *Marrubium deserti* de Noé, an endemic Algerian Lamiaceae. *Phytotherapie* 2010; 8: 353–358
- [91] Davies-Coleman MT, Rivett DEA. Transformation of hispanolone from *Ballota africana* into 15, 16-epoxy-9-hydroxy-labdane-13(16), 14-diene. *S Afr J Chem* 1990; 43: 117–119
- [92] Savona G, Piozzi F, Rodriguez B. Hispanolone, a new furanoditerpene. *Heterocycles* 1978; 9: 257–261
- [93] Seidel V, Bailleul F, Tillequin F. Isolation from *Ballota nigra* L. of 13-hydroxyballonigrinolide, a diterpene useful for the standardization of the drug. *J Pharm Belg* 1996; 51: 72–73
- [94] Seidel V, Bailleul F, Tillequin F. Diterpene et esters heterosidiques phenylpropanoiques de *Ballota nigra*. *Ann Pharm Fr* 1998; 56: 31–35
- [95] Savona G, Piozzi F, Hanson JR, Siverns M. 18-Hydroxyballonigrin, a new diterpenoid from *Ballota acetabulosa*. *J Chem Soc Perkin I* 1978: 1271–1272
- [96] Bruno M, Bondí ML, Piozzi F, Arnold NA, Simmonds MSJ. Occurrence of 18-hydroxyballonigrin in *Ballota saxatilis* ssp. *saxatilis* from Lebanon. *Biochem System Ecol* 2001; 29: 429–431
- [97] Rustaiyan A, Mosslemin-Kupaii MH, Habibi Z. Two new diterpenes from *Ballota aucheri*. *Iran J Chem Chem Eng* 1991; 10: 72–77
- [98] Ali MS, Amina M, Al-Lohedan HA, Al Musayeib NM. Human serum albumin binding to the biologically active labdane diterpene “leoheterin”: spectroscopic and in silico analysis. *J Photochem Photobiol B* 2018; 182: 9–17
- [99] Balansard J. The lactone of some Labiatae. *C R Seances Soc Biol* 1934; 117: 1014–1015
- [100] Tesso H, König WA. Terpenes from *Otostegia integrifolia*. *Phytochemistry* 2004; 65: 2057–2062
- [101] Endale A, Bisrat D, Animut A, Bucar F, Asres K. *In vivo* antimalarial activity of a labdane diterpenoid from the leaves of *Otostegia integrifolia* Benth. *Phytother Res* 2013; 27: 1805–1809
- [102] Bruno M, Savona G, Pascual C, Rodríguez B. Preleoisibirin, a prefuranic labdane diterpene from *Ballota nigra* subsp. *foetida*. *Phytochemistry* 1986; 25: 538–539
- [103] Savona G, Piozzi F, Marino M. Rupestralic acid, a new lactone. *Heterocycles* 1977; 7: 161–164
- [104] Rodriguez B, Savona G, Piozzi F. Two new unusual diterpenoids from *Ballota hispanica*. *J Org Chem* 1979; 44: 2219–2221
- [105] López de Lerma J, García-Blanco S, Rodríguez JG. New compounds from *Ballota hispanica*. X-ray crystal and molecular structure of hispanonic acid methyl ester. *Tetrahedron Lett* 1980; 21: 1273–1274
- [106] Riaz M, Krohna K, Malik A, Flörke U. Limbetazulone: a new ‘decahydro-8-oxanaphtho[2, 1-f]-azulen-7-one’ diterpenoid from *Ballota limbata*, and occurrence of two conformational isomers in the crystal. *Chem Biodivers* 2004; 1: 458–462
- [107] Ahmad VU, Farooq U, Abbaskhan A, Hussain J, Abbasi MA, Nawaz SA, Choudhary MI. Four new diterpenoids from *Ballota limbata*. *Helv Chim Acta* 2004; 87: 682–689
- [108] Ayatollahi SA, Kobarfard F, Asgarpanah J, Rahmati Roodsari M, Fanai Gh, Iqbal Choudhary M. Diterpenoids of *Otostegia persica* (Burm.) Boiss. *DARU J Pharm Sci* 2009; 17: 290–293
- [109] Farooq U, Khan A, Ahmad VU, Khan SS, Kousar F, Arshad S. Two new rare-class tetracyclic diterpenoids from *Otostegia limbata*. *Chem Pharm Bull* 2007; 55: 471–473
- [110] Ahmad VU, Farooq U, Hussain J, Ullah F, Nawaz SA, Choudhary MI. Two new diterpenoids from *Ballota limbata*. *Chem Pharm Bull* 2004; 52: 441–443
- [111] Farooq U, Khan A, Ahmad VU, Azhar-UI-Haq, Khan SS, Farooq R, Pervez A, Shah MM. Complete <sup>1</sup>H and <sup>13</sup>C NMR assignments of two new *trans*-clerodane diterpenoids from *Otostegia limbata*. *Magn Reson Chem* 2007; 45: 766–769
- [112] Ahmad VU, Khan A, Farooq U, Kousar F, Khan SS, Nawaz SA, Abbasi MA, Choudhary MI. Three new cholinesterase-inhibiting *cis*-clerodane diterpenoids from *Otostegia limbata*. *Chem Pharm Bull* 2005; 53: 378–381
- [113] Ahmad VU, Khan A, Farooq U, Kousar F, Khan SS, Hussain J. Two new *trans*-clerodane diterpenoids from *Otostegia limbata*. *J Asian Nat Prod Res* 2007; 9: 91–95
- [114] Farooq U, Khan A, Ahmad VU, Kousar F, Iqbal S. Limbatolide F and G: two new *trans*-clerodane diterpenoids from *Otostegia limbata*. *Polish J Chem* 2005; 79: 1757–1762
- [115] Tóth E, Tóth G, Máthé I, Blunden G. Martynoside, forsythoside B, lada-nein and 7 $\alpha$ -acetoxyroyleanone from *Ballota nigra* L. *Biochem System Ecol* 2007; 35: 894–897
- [116] Kumar S, Dobhal MP, Joshi BC, Baror FSK. Chemical investigation and pharmacological screening of *Roylea elegans* Wall. Part Wall. Part II. *Herba Polonica* 1981; 27: 99–102
- [117] Shabnam Habib R, Jamshaid M, Tahir MN, Khan TJ, Khan IU. (4R,5R,6S,7R,8S,9R,10S,13S)-7,8 $\beta$ -Epoxy-momilactone-A. *Acta Crystallogr E* 2008; 64: o892
- [118] Gray CA, Rivett DEA, Davies-Coleman MT. The absolute stereochemistry of a diterpene from *Ballota aucheri*. *Phytochemistry* 2003; 63: 409–413
- [119] Harrison LJ, Asakawa Y. Methyl verticoate, a novel diterpenoid with an unusual carbon skeleton from the conifer *Sciadopitys verticillata*. *J Chem Res* 1988; 10: 340–341

- [120] Wu SJ, Chan HH, Hwang TL, Qian K, Morris-Natschke S, Lee KH, Wu TS. Salviatalin A and salvitrijudin A, two diterpenes with novel skeletons from roots of *Salvia digitaloides* and anti-inflammatory evaluation. *Tetrahedron Lett* 2010; 51: 4287–4290
- [121] Wu SJ, Huang CH, Chan YY, Liao YR, Hwang TL, Wu TS. Two diterpenoids and a cyclopenta[c]pyridine derivative from roots of *Salvia digitaloids*. *Int J Mol Sci* 2014; 15: 11566–11577
- [122] Wang LX, Fang YD, Zhang RH, Ren FC, Zhang XJ, Wang F, Xiao WL. Hispanane-type diterpenoid and secoiridoid glucosides from *Viburnum cylindricum*. *Chem Biodivers* 2018; 15: e1700418
- [123] Herz W, Prasad JS, Mohanraj S. Cationic cyclizations and rearrangements as models for strobane and hispanane biogenesis. *J Org Chem* 1983; 48: 81–90
- [124] Karioti A, Heilmann J, Skaltsa H. Labdane diterpenes from *Marrubium velutinum* and *Marrubium cylleneum*. *Phytochemistry* 2005; 66: 1060–1066
- [125] Hersel U, Steck M, Seifert K. A new route to 2,7- and 7-functionalized labdanes. *Eur J Org Chem* 2000: 1609–1615
- [126] Tasdemir D, Wright AD, Sticher O. New furanoid and seco-labdanoid diterpenes from *Leonurus persicus*. *J Nat Prod* 1996; 59: 131–134
- [127] Hussein AA, Meyer MJJ, Rodriguez B. Complete <sup>1</sup>H and <sup>13</sup>C NMR assignments of three labdane diterpenoids isolated from *Leonotis ocyimifolia* and six other related compounds. *Magn Reson Chem* 2003; 41: 147–151
- [128] El Bardai S, Morel N, Wibo M, Fabre N, Llabras G, Lyoussi B, Quetin-Leclercq J. The vasorelaxant activity of marrubenol and marrubin from *Marrubium vulgare*. *Planta Med* 2003; 69: 75–77
- [129] Rigano D, Aviello G, Bruno M, Formisano C, Rosselli S, Capasso R, Senatore F, Izzo AA, Borrelli F. Antispasmodic effects and structure-activity relationship of labdane diterpenoids from *Marrubium globosum* ssp. *libanoticum*. *J Nat Prod* 2009; 72: 1477–1481
- [130] Tesso H. Isolation and Structure Elucidation of natural Products from Plants [Dissertation]. Hamburg: University of Hamburg, Institute of Organic Chemistry; 2005
- [131] Rodriguez B, Savona G. Complete assignments of <sup>1</sup>H and <sup>13</sup>C NMR spectra of four hispanane diterpenoids. *Magn Reson Chem* 2000; 38: 802–804
- [132] Saeidnia S, Ghamarinia M, Gohari AR, Shaker A. Terpenes from the root of *Salvia hypoleuca* Benth. *DARU J Pharm Sci* 2012; 20: 66
- [133] Wellsow J, Grayer JR, Veitch NC, Kokubun T, Lelli R, Kite GC, Simmonds MSJ. Insect-antifeedant and antibacterial activity of diterpenoids from species of *Plectranthus*. *Phytochemistry* 2006; 67: 1818–1825
- [134] Meriçli AH, Meriçli F, Tuzlacı E. Flavonoids of *Ballota acetabulosa*. *Acta Pharmaceutica Turcica* 1988; 30: 143–144
- [135] Askun T, Tekwu EM, Satil F, Modanlıoğlu S, Aydeniz H. Preliminary antimicrobial study on selected Turkish plants (Lamiaceae) against *Mycobacterium tuberculosis* and search for some phenolic constituents. *BMC Complement Altern Med* 2014; 13: 365
- [136] Ferreres F, Tomas-Barberan FA, Tomas-Lorente F. Flavonoid compounds from *Ballota hirsuta*. *J Nat Prod* 1986; 49: 554–555
- [137] Tomás-Barberan FA, Gil MI, Ferreres F, Tomás-Lorente F. Flavonoid p-coumaroylglucosides and 8-hydroxyflavone allosylglucosides in some Labiatae. *Phytochemistry* 1992; 31: 3097–3102
- [138] Jiang S, Bai XR, Zou DZ, Wang P, Zhang L, Long P, Zhang CH, He YL, Li ZH, Li MH. Chemical constituents from *Panzeria alaschanica* Kupr. (Labiatae). *Biochem System Ecol* 2015; 61: 268–270
- [139] Zhukov IM, Belikov VV. Chromatospectrophotometric determination of flavonoids and dioxycinnamic acids in the above-ground part of *Ballota nigra* L. *Farmatsevtichnii Zhurnal* (Kiev) 1989; 5: 55–58
- [140] Ku CT, Chen SC, Wang JP, Wu JB, Kuo SC. Studies on anti-inflammatory constituents of *Leucas mollissima* Wall. var. *chinensis* Benth. *Chin Pharm J* 2000; 52: 261–273
- [141] Tofighi Z, Alipour F, Hadavinia H, Abdollahi M, Hadjiakhoondi A, Yassa N. Effective antidiabetic and antioxidant fractions of *Otostegia persica* extract and their constituents. *Pharm Biol* 2014; 52: 961–966
- [142] Tofighi Z, Alipour F, Goodarzy S, Yassa N, Hadjiakhoondi A, Hadavinia H. Phytochemical and antidiabetic investigations of *Otostegia persica* essential oil from Iran. *Planta Med* 2009; 75: 1013–1014
- [143] Hou FF, Zheng YF, Zhang HM, Shen SM, Du SS. Chemical constituents in *Panzeria alaschanica* Kupr. *Zhongguo Shiyan Fangjixue Zazhi* 2009; 15: 18–20
- [144] Wang QH, Hu YR, Shao CY, Wu JS, Han NRCKT, Dai NYT, Wu RJ. Anti-inflammatory effect and high performance liquid chromatography (HPLC) analysis of the EtOAc extract from *Panzeria alaschanica*. *Afr J Pharm Pharmacol* 2015; 9: 974–981
- [145] Shao C, Wang Q, Wu R, Wu J, Han N, Dai N. Study on chemical constituents of *Panzeria alaschanica*. *J Chin Med Mat* 2015; 38: 1668–1670
- [146] Çitoglu G, Tanker M, Sever B. Flavonoid aglycones from *Ballota saxatilis* subsp. *saxatilis*. *Pharm Biol* 1999; 37: 158–160
- [147] Çitoğlu GS, Sever B, Antus S, Baitz-Gács E, Altanlar N. Antifungal flavonoids from *Ballota glandulosissima*. *Pharm Biol* 2003; 41: 483–486
- [148] Abdelshafeek KA, Daboob AA. Investigation of flavonoids and antimicrobial activity of *Ballota andreuziana*. *Pharmacogn Mag* 2009; 5: 203–208
- [149] Abdelshafeek KA, Elgendy HA, El Missiry MM, Seif El Nasr MM. Structure elucidation of phenolic acids, flavonoids and hypocholesterolemic activity of *Nepeta septemcrenata* and *Otostegia fruticosa*. *Der Pharma Chem* 2016; 8: 357–362
- [150] Siciliano T, Bader A, Vassallo A, Braca A, Morelli I, Pizza C, De Tommasi N. Secondary metabolites from *Ballota undulata*. *Biochem System Ecol* 2005; 33: 341–351
- [151] Ikram M, Jehangir S, Razaq S, Kawano M. Chemical investigation of *Otostegia limbata*. *Planta Med* 1978; 37: 189–190
- [152] Parvez M, Riaz M, Malik A. Eupatorin. *Acta Crystallogr E* 2001; E57: o289–o291
- [153] Ayatollahi SAM, Kobarfard F, Asgarpanah J, Choudhary MI. Antiglycation activity of *Otostegia persica* (Burm.) Boiss. *Afr J Biotechnol* 2010; 9: 3645–3648
- [154] Ansari S, Joshi YC, Dobhal MP, Joshi BC. Chemical constituents of the stem of *Roylea elegans* Wall. *Pharmazie* 1982; 37: 70–71
- [155] Kisiel W, Piozzi F. Tangeretin from *Ballota nigra*. *Polish J Chem* 1995; 69: 476–477
- [156] Aboutabl EA, Sokkar NM, Awaad AS. Phytochemical study of *Otostegia fruticosa* (Forssk.) and biological activity. *Bull Fac Pharm Cairo Univ* 2000; 38: 115–118
- [157] Ghedadba N, Hambaba L, Ayachi A, Aberkane MC, Bousselfa H, Ouel-Mokhtar SM. Polyphenols content, antioxidant and antimicrobial activities of leaf extracts of *Marrubium deserti* de Noé ex Coss. *Phytotherapie* 2015; 13: 118–129
- [158] Yassa N, Sharififar F, Shafiee A. *Otostegia persica* as a source of natural antioxidants. *Pharm Biol* 2005; 43: 33–38
- [159] Uysal S, Aumeeruddy-Elalfi Z, Zengin G, Aktumsek A, Mocan A, Custodio L, Neng NR, Nogueira JMF, Ćirić A, Glamočlija J, Soković M, Mahomoodally MF. Insight into the biological properties and phytochemical composition of *Ballota macrodonta* Boiss. et Balansa, – an endemic medicinal plant from Turkey. *Ind Crops Prod* 2018; 113: 422–428
- [160] Shrififar F, Yassa N, Shafiee A. Antioxidant activity of *Otostegia persica* (Labiatae) and its constituents. *Iran J Pharm Res* 2003; 2: 235–239
- [161] Sahpaz S, Skaltsounis AL, Bailleul F. Polyphenols from *Ballota acetabulosa*. *Biochem System Ecol* 2002; 30: 601–604
- [162] Hennebelle T, Sahpaz S, Ezer N, Bailleul F. Polyphenols from *Ballota larendana* and *Ballota pseudodictamnus*. *Biochem System Ecol* 2008; 36: 441–443

- [163] Darbour N, Baltassat F, Raynaud J. The presence of an O-heteroside and a C-heteroside of apigenine in leaves of *Ballota-foetida* Lamk (Labiatae). *Pharmazie* 1986; 41: 605–606
- [164] Radwan HM, El-Missiry MM, El-Nasr MM. Phytochemical investigation of *Ballota undulata* Benth. *Bull Fac Pharm Cairo Univ* 1997; 35: 83–86
- [165] Ranganayaki S, Gusain PS, Sigh AK. The chemical constituents of leaves of *Roylea elegans*. *J Sci Res Plants Med* 1985; 6: 5–9
- [166] Tofighi Z, Ostad SN, Khezrrahdoost S, Salehizadeh H, Yassa N. Potent anti-nociceptive and anti-inflammatory effects of methanol fraction of *Otostegia persica* extract and its components. *Res J Pharmacogn* 2017; 4: 23–29
- [167] Khan A, Ahmad VU, Farooq U, Bader S, Arshad S. Two new flavonol glycosides from *Otostegia limbata* Benth. *Chem Pharm Bull* 2009; 57: 276–279
- [168] Wang QH, Wu JS, Wu RJ, Han NRCKT, Dai NYT. Anti-inflammatory effect and isolation of phenylethanoid and acylated flavone glycosides from *Panzeria alaschanica*. *Z Naturforsch B Chem Sci* 2015; 70: 379–384
- [169] Bao ML, Wang QH, Hao JS. *In vivo* antioxidative activity of 5,7,4'-trihydroxyflavone-7-O-(6''-O-[E]-coumaroyl)- $\beta$ -glucopyranoside isolated from *Panzeria alaschanica*. *Afr J Pharm Pharmacol* 2017; 11: 567–572
- [170] Bertrand MC, Tillequin F, Bailleul F. Two major flavonoids from *Ballota nigra*. *Biochem System Ecol* 2000; 28: 1031–1033
- [171] Noor AT, Fatima I, Ahmad I, Malik A, Afza N, Iqbal L, Latif M, Khan SB. Leufolins A and B, potent butyrylcholinesterase-inhibiting flavonoid glucosides from *Leucas urticifolia*. *Molecules* 2007; 12: 1447–1454
- [172] Khan A, Ahmad VU, Farooq U. Two new acylated flavonol glycosides from the roots of *Otostegia limbata*. *Helv Chim Acta* 2009; 92: 731–739
- [173] Wang Q, Wu J, Wu X, Tai W, Dai N, Wu R, Han N. Anti-inflammatory and analgesic effects of two new flavone C-glycosides from *Panzeria alaschanica*. *Monatsh Chem* 2015; 146: 1025–1030
- [174] Anwar KJ, Mosihuzaman M, Nahar N, Khan SH, Rashid R, Sultana N. Chemical studies of anti-hyperglycemic active extract of *Otostegia aucheri* Boiss. *J Bangladesh Chem Soc* 2004; 17: 18–22
- [175] Abdelshafeek K, Elgendy HA, ElMissiry MM, Seif ELNasr MM. Isolation and identification of some chemical constituents and antimicrobial activity of two Lamiaceae plants growing in Saini. *Egypt J Chem* 2016; 59: 21–31
- [176] Dobhal MP, Joshi BC. Chemical investigations of *Roylea elegans* Wall. Part I. *Herba Polonica* 1979; 25: 95–97
- [177] Ayatollahi SAM, Kobarfard F, Asgarpanah J, Ahmed Z. Chemical constituents from *Otostegia persica*. *J Chem Soc Pak* 2007; 29: 61–63
- [178] Majumder PL, Maiti RN, Panda SK, Mal D, Raju MS, Wenkert E. Structure of moronic acid. *J Org Chem* 1979; 44: 2811–2812
- [179] Janicsak G, Veres K, Zoltan Kakasy A, Mathe I. Study of the oleanolic and ursolic acid contents of some species of the Lamiaceae. *Biochem System Ecol* 2006; 34: 392–396
- [180] Ranganayaki S, Gusain PS, Singh AK. Isolation and study of a pentacyclic triterpene from the roots of *Roylea elegans* Wall. *J Sci Res Plants Med* 1979; 1: 44–47
- [181] Fatima I, Ahmad I, Anis I, Malik A, Afza N, Iqbal L, Latif M. New butyrylcholinesterase inhibitory steroid and peroxy acid from *Leucas urticifolia*. *Arch Pharm Res* 2008; 31: 999–1003
- [182] Bhatt UP, Sati SC, Bahuguna RP, Semwal RB, Semwal DK. Two antidiabetic constituents from *Roylea cinerea* (D. Don) Baill. *Nat Prod Res* 2018; 32: 1281–1286
- [183] Popa DP, Pasechnik GS. Higher terpenoids of some species of Labiatae. *Chem Nat Compd* 1974; 10: 529–530
- [184] Dixit V, Irshad S, Singh H, Agnihotri P, Husain T, Khatoun S. High-performance thin-layer chromatographic determination of three therapeutic phenolic components in *Leucas* species. *J Planar Chromatogr – Modern TLC* 2017; 30: 25–31
- [185] Vrchovska V, Spilkova J, Valentao P, Sousa C, Andrade PB, Seabra RM. Antioxidative properties and phytochemical composition of *Ballota nigra* infusion. *Food Chem* 2007; 105: 1396–1403
- [186] Tóth E, Janicsák G, Máthé I, Blunden G. Determination of phenylpropanoids in three *Ballota* species. *J Planar Chromatogr – Modern TLC* 2009; 22: 293–296
- [187] Didry N, Seidel V, Dubreuil L, Tillequin F, Bailleul F. Isolation and antibacterial activity of phenylpropanoid derivatives from *Ballota nigra*. *J Ethnopharmacol* 1999; 67: 197–202
- [188] Blunden G, Yang MHE, Yuan ZX, Smith BE, Patel A, Cegarra JA, Mathé I, Janicsák G. Betaine distribution in the Labiatae. *Biochem System Ecol* 1996; 24: 71–81
- [189] Janicsák G, Tóth E, Máthé I. TLC-densitometric investigations of phenylpropanoid glycosides in black horehound (*Ballota nigra* L.). *J Planar Chromatogr – Modern TLC* 2007; 20: 443–446
- [190] Tipirdamaz R, Guvenc A. Seed fatty acids composition of *Ballota cristata*. *Chem Nat Compd* 2004; 40: 291–292
- [191] Balansard J. Pharmacological study of *Ballota foetida*. *C R Seances Soc Biol* 1934; 115: 1295–1297
- [192] Khokhrina TA, Peshkova VA. Stachydrine from *Phlomis tuberosa* and *Panzeria lanata*. *Chem Nat Compd* 1975; 10: 284
- [193] Seidel V, Bailleul F, Tillequin F. Phenylpropanoid glycosides from *Ballota nigra*. *Planta Med* 1996; 62: 186–187
- [194] Seidel V, Bailleul F, Libot F, Tillequin F. A phenylpropanoid from *Ballota nigra*. *Phytochemistry* 1997; 44: 691–693
- [195] Pedersen JA. Distribution and taxonomic implications of some phenolics in the family Lamiaceae determined by ESR spectroscopy. *Biochem System Ecol* 2000; 28: 229–253
- [196] Ertas A, Boğa M, Yeşil Y. Phytochemical profile and ABTS cation radical scavenging, cupric reducing antioxidant capacity and anticholinesterase activities of endemic *Ballota nigra* L. subsp. *anatolica* P.H. Davis from Turkey. *J Coast Life Med* 2014; 2: 555–559
- [197] Pialt L. The lactone of some Labiatae. *J Pharm Chim* 1911; 1: 248–255
- [198] Kolisnyk Y, Ochkur O, Kovalyova A, Koshoviy O. Organic acids of vegetative and generative organs of black horehound. *Pharma Innovation* 2014; 3: 33–37
- [199] Marin PD, Sajdl V, Kapor S, Tatic B, Petkovic B, Duletic S. Fatty acids of the Stachyoideae. *Biochem System Ecol* 1992; 20: 389–392
- [200] Abdelshafeek KA, Elgattar AA, Zarkoon AH, Alwahash MA, Shahat AA. Investigation of the volatile oils, lipid constituents and biological activity of *Ballota andreuzziiana*, *Teucrium zanonii* and *Verbena tenuisecta* in Libya. *Asian Pac J Tropical Med* 2010; 3: 594–601
- [201] Rustaiyan A, Masoudi S, Ameri N, Samiee K, Monfared A. Volatile constituents of *Ballota aucheri* Boiss., *Stachys benthamiana* Boiss. and *Perovskia abrotanoides* Karel. growing wild in Iran. *J Ess Oil Res* 2006; 18: 218–221
- [202] Laouer H, Yabrir B, Djeridane A, Yousfi M, Beldovini N, Lamamra M. Composition, antioxidant and antimicrobial activities of the essential oil of *Marrubium deserti*. *Nat Prod Commun* 2009; 4: 1133–1138
- [203] Chebrouk F, Hadj Mohammed M. Composition des huiles essentielles de *Marrubium deserti* de Noe de la region de Ghardaïa. *Annales de la Faculté des Sciences et Sciences de l'Ingénieur* 2009; 1: 75–81
- [204] Chemsas AE, Zellagui A, Öztürk M, Erol E, Ceylan O, Duru ME, Gherraf N. Antibiofilm formation, antioxidant and anticholinesterase activities of essential oil and methanol extract of *Marrubium deserti* de Noé. *J Mater Environ Sci* 2018; 7: 993–1000
- [205] Riccobono L, Ben Jemia M, Senatore F, Bruno M. Chemical composition and biological activity of the essential oil of *Ballota hispanica* (L.) Benth. growing wild in Sicily. *Plant Biosyst* 2016; 150: 1065–1071
- [206] Todorova M, Altantsetseg S, Trendafilova A, Shatar S. Chemical composition of *Panzeria lanata* (L.) Bunge essential oil from Mongolian Gobi. *J Ess Oil-Bearing Plants* 2013; 16: 257–260

- [207] Đorđević AS, Jovanović OP, Zlatković BK, Stojanović GS. Chemical composition of *Ballota macedonica* Vandas and *Ballota nigra* L. ssp. *foetida* (Vis.) Hayek essential oils – the chemotaxonomic approach. *Chem Biodivers* 2016; 13: 782–788
- [208] Morteza-Semnani K, Saeedi M, Akbarzadeh M. The essential oil composition of *Ballota nigra*. *Chem Nat Compd* 2007; 43: 722–723
- [209] Vukovic N, Sukdolac S, Solujic S, Niciforovic N. Antimicrobial activity of the essential oil obtained from roots and chemical composition of the volatile constituents from the roots, stems, and leaves of *Ballota nigra* from Serbia. *J Med Food* 2009; 12: 435–441
- [210] Jamzad M, Rustaiyan A, Jamzad Z, Masoudi S. Essential oil composition of *Salvia indica* L., *Thymus caucasicus* Wind. Ex Ronniger subsp. *grossheimii* (Ronniger) Jalas. and *Ballota nigra* L. three Labiatae species from Iran. *J Ess Oil Bearing Plants* 2011; 14: 76–83
- [211] Kolisnyk YS, Kovaleva AM, Goryacha OV. The study of the volatile oils composition obtained from vegetative and generative organs of *Ballota nigra* L. *Visnik Farmatsii* 2014; 78: 59–62
- [212] Karemizadeh Z, Amini T, Nazari F, Habibi Z. Volatile constituents of *Ballota nigra* subsp. *anatolica* from Iran. *Chem Nat Compd* 2009; 45: 737–738
- [213] Sarikaya AG. Volatile component composition of *Ballota nigra* subsp. *anatolica* at different vegetation periods in Çamlica province of Kütahya city, Turkey. *Appl Ecol Env Res* 2017; 15: 1929–1933
- [214] Kaya A, Kürkçüoğlu M, Dinç M, Doğu S. Compositions of the essential oils of *Ballota nigra* subsp. *uncinata* and subsp. *anatolica* from Turkey. *Indian J Pharm Educ Res* 2017; 51: S185–S189
- [215] Bader A, Caponi C, Cioni PL, Flamini G, Morelli I. Composition of the essential oil of *Ballota undulata*, *B. nigra* ssp. *foetida* and *B. saxatilis*. *Flavour Fragr J* 2003; 18: 502–504
- [216] Fraternali D, Bucchini A, Giampieri L, Ricci D. Essential oil composition and antimicrobial activity of *Ballota nigra* L. ssp. *foetida*. *Nat Prod Commun* 2009; 4: 585–588
- [217] Fraternali D, Ricci D. Essential oil composition and antifungal activity of aerial parts of *Ballota nigra* ssp. *foetida* collected at flowering and fruiting times. *Nat Prod Commun* 2014; 9: 1015–1018
- [218] Rigano D, Marrelli M, Formisano C, Menichini F, Senatore F, Bruno M, Conforti F. Phytochemical profile of three *Ballota* species essential oils and evaluation of the effects on human cancer cells. *Nat Prod Res* 2017; 31: 436–444
- [219] Majdi M, Dastan D, Maroofi H. Chemical composition and antimicrobial activity of essential oils of *Ballota nigra* subsp. *kurdica* from Iran. *Jundishapur J Nat Pharm Prod* 2017; 12: e36314
- [220] Couladis M, Chinou IB, Tzakou O, Loukis A. Composition and antimicrobial activity of the essential oil of *Ballota pseudodictamnus* L. Benth. *Phytother Res* 2002; 16: 723–726
- [221] Erdogan EA, Everest A, Sonmez Ö. Antimicrobial activity of the essential oil of *Ballota saxatilis* subsp. *brachyodonta* (Boiss) P. H. Davis & Doroszenko from Turkey. *J Ess Oil Bearing Plants* 2014; 17: 1100–1104
- [222] Awadh Ali NA, Alhamzy EH, Chhetri BK, Dosoky NS, Setzer WN. Chemical composition, antimicrobial, and cytotoxic activities of the essential oil of *Otostegia fruticosa* subsp. *schimperii* from Yemen. *Nat Prod Commun* 2017; 12: 969–972
- [223] Özek T, Tabanca N, Demirci F, Wedge DE, Başer KHC. Enantiomeric distribution of some linalool containing essential oils and their biological activities. *Rec Nat Prod* 2010; 4: 180–192
- [224] Aboutabl EA, Sokkar NM, Megid RMA, De Pooter HL, Masoud H. Composition and antimicrobial activity of *Otostegia fruticosa* Forssk. oil. *J Ess Oil Res* 1995; 7: 299–303
- [225] Karami A, Esmaeili H, Shahbazian D. Essential oil composition of *Rydingia michauxii* (Briq.) Scheen & V.A. Albert endemic of Iran. *Nat Prod Res* 2018; 32: 229–233
- [226] Javidnia K, Miri R, Soltani M, Khosravi AR. Chemical constituents of the essential oil of *Otostegia michauxii* Briq. from Iran. *J Ess Oil Res* 2010; 22: 1–2
- [227] Javidnia K, Miri R, Soltani M. Essential oil composition of *Otostegia persica* Boiss. from Iran. *J Ess Oil Res* 2010; 22: 609–610
- [228] Tofighi Z, Alipour F, Yassa N, Hadjiakhoondi A, Hadavinia H, Goodarzi S, Golestani R. Chemical composition and antioxidant activity of *Otostegia persica* essential oil from Iran. *Int J Essen Oil Ther* 2009; 3: 45–48
- [229] Shariffar F, Mozaffarian V, Moradkhani S. Comparison of antioxidant and free radical scavenging activities of the essential oils from flowers and fruits of *Otostegia persica* Boiss. *Pak J Biol Sci* 2007; 10: 3895–3899
- [230] Erdogan-Orhan I, Sever-Yılmaz B, Altun ML, Saltan G. Radical quenching activity, ferric-reducing antioxidant power, and ferrous ion-chelating capacity of 16 *Ballota* species and their total phenol and flavonoid contents. *J Med Food* 2010; 13: 1537–1543
- [231] Citoglu GS, Çoban T, Sever B, Işcan M. Antioxidant properties of *Ballota* species growing in Turkey. *J Ethnopharmacol* 2004; 92: 275–280
- [232] Rashid R, Murtaza G, Khan AK, Mir S. Antioxidant and hypoglycemic effect of *Otostegia aucheri* methanolic extract in streptozotocin-induced diabetic male Long-Evans rats. *Acta Pol Pharm* 2014; 71: 631–635
- [233] Sharma R, Yadav D, Asif M, Jayasri MA, Agnihotri VK, Ravikumar PC. Antidiabetic and antioxidant activities of *Roylea cinerea* extracts: a comparative study. *Indian J Exp Biol* 2017; 55: 611–621
- [234] Kechar K, Hellal B. Evaluation of the antioxidant activity of extracts of *Ballota hirsuta* Benth. from Tessala (Western Algeria). *Phytotherapie* 2017; 15: 217–221
- [235] Makowczynska J, Grzegorzczak-Karolak I, Wysokinska H. Antioxidant activity of tissue culture-raised *Ballota nigra* L. plants grown *ex vitro*. *Acta Pol Pharm* 2015; 72: 769–775
- [236] Daels-Rakotoarison DA, Seidel V, Gressier B, Brunet C, Tillequin F, Bailleul F, Luycx M, Dine T, Cazin M, Cazin JC. Neurosedative and antioxidant activities of phenylpropanoids from *Ballota nigra*. *Arzneimittelforschung* 2000; 50: 16–23
- [237] Seidel V, Verholle M, Malard Y, Tillequin F, Fruchart JC, Duriez P, Bailleul F, Teissier E. Phenylpropanoids from *Ballota nigra* L. Inhibit *in vitro* LDL Peroxidation. *Phytother Res* 2000; 14: 93–98
- [238] Gursoy N, Tepe B. Determination of the antimicrobial and antioxidative properties and total phenolics of two “endemic” Lamiaceae species from Turkey: *Ballota rotundifolia* L. and *Teucrium chamaedrys* C. Koch. *Plant Foods Hum Nutr* 2009; 64: 135–140
- [239] Couladis M, Tzakou O, Verykokidou E, Harvala C. Screening of some Greek aromatic plants for antioxidant activity. *Phytother Res* 2003; 17: 194–195
- [240] Chekol YA, Desta ZY. Determination of antioxidant and antimicrobial activities of leaf extracts of *Otostegia integrifolia*. *Chem Cent J* 2018; 12: 63
- [241] Waheed I, Ahmad M, Syed NH, Ashraf R. Investigation of phytochemical and antioxidant properties of methanol extract and fractions of *Ballota limbata* (Lamiaceae). *Indian J Pharm Sci* 2014; 76: 251–256
- [242] Ahmed D, Arshad MA, Asghar MN, Aujla MI. Antioxidant and free radical scavenging potential of *Otostegia limbata*. *Asian J Chem* 2010; 22: 4524–4532
- [243] Moein S, Pimoradloo E, Moein M, Vessal M. Evaluation of antioxidant potentials and  $\alpha$ -amylase inhibition of different fractions of Labiatae plants extracts: as a model of antidiabetic compounds properties. *Biomed Res Int* 2017; 7319504: 1–8
- [244] Safaeian L, Yaghoobi S, Javanmard SH, Ghasemi-Dehkordi N. The effect of hydroalcoholic extract of *Otostegia persica* (Burm.) Boiss. against H<sub>2</sub>O<sub>2</sub>-induced oxidative stress in human endothelial cells. *Res J Pharmacol* 2017; 4: 51–58



- [245] Özbek H, Çitoğlu GS, Dülger H, Uğraş S, Sever B. Hepatoprotective and anti-inflammatory activities of *Ballota glandulosissima*. J Ethnopharmacol 2004; 95: 143–149
- [246] Yilmaz BS, Özbek H, Çitoğlu GS. Antinociceptive and anti-inflammatory activities of *Ballota inaequidens*. Pharm Biol 2006; 44: 636–641
- [247] Elmezogi J, Zetrini A, Ben-Hussein G, Anwar M, Gbaj A, El-Ashheb M, Nahar L, Sarker SD. Evaluation of anti-inflammatory activity of some Libyan medicinal plants in experimental animals. Arch Biol Sci 2012; 64: 1058–1064
- [248] Nabil G, Leila H. Anti-inflammatory and analgesic activities of methanolic extract from *Marrubium deserti* leaves and evaluation of their acute toxicity. Pharm Lett 2016; 8: 33–40
- [249] Dulger B, Kilcik MA. Antibacterial activity of *Ballota acetabulosa* against methicillin-resistant *Staphylococcus aureus*. Asian J Chem 2011; 23: 416–418
- [250] Dulger B, Dulger G. Antimicrobial activity of the leaves of *Ballota acetabulosa* on microorganisms isolated from urinary tract infection. Turk J Pharm Sci 2012; 9: 257–262
- [251] Cock IE, van Vuuren SF. The potential of selected South African plants with anti-*Klebsiella* activity for the treatment and prevention of *Ankylosing spondylitis*. Inflammopharmacology 2014; 23: 21–35
- [252] Quave CL, Plano LRW, Bennett BC. Quorum sensing inhibitors of *Staphylococcus aureus* from Italian medicinal plants. Planta Med 2011; 77: 188–195
- [253] Ullah N, Ahmad I, Ayaz S. *In vitro* antimicrobial and antiprotozoal activities, phytochemical screening and heavy metals toxicity of different parts of *Ballota nigra*. BioMed Res Int 2014: 321803
- [254] Quave CL, Plano LRW, Pantuso T, Bennett BC. Effects of extracts from Italian medicinal plants on planktonic growth, biofilm formation and adherence of methicillin-resistant *Staphylococcus aureus*. J Ethnopharmacol 2008; 118: 418–428
- [255] Dulger G, Aki C, Dulger B. Antimicrobial activity of endemic *Ballota nigra* subsp *anatolica* in Turkey. Asian J Chem 2010; 22: 6497–6502
- [256] Dulger G, Dulger B. Antibacterial activity of endemic *Ballota nigra* subsp. *anatolica* against some human eye pathogens from Turkey. Int J Life Sci 2017; 5: 1–3
- [257] Ullah N, Ahmad I, Ahmad NF. *In vitro* antimicrobial, antiprotozoal activities and heavy metals toxicity of different parts of *Ballota pseudodictamnus* (L.) Benth. Pak J Pharm Sci 2017; 30: 2203–2209
- [258] Kahaliw W, Aseffa A, Abebe M, Teferi M, Engidawork E. Evaluation of the antimycobacterial activity of crude extracts and solvent fractions of selected Ethiopian medicinal plants. BMC Complement Altern Med 2017; 17: 143
- [259] Anwar N, Salik S, Ahmad D. Antibacterial activity of *Otostegia limbata*. Int J Agric Biol 2009; 11: 647–650
- [260] Javidnia K, Miri R, Assadollahi M, Gholami M, Ghaderi M. Screening of selected plants growing in Iran for antimicrobial activity. Iran J Sci Technol A 2009; 33: 329–333
- [261] Asghari G, Nourallahi H, Havaie SA, Issa L. Antimicrobial activity of *Otostegia persica* Boiss. extracts. Res Pharm Sci 2006; 1: 53–58
- [262] Nelson K, Lyles JT, Li T, Saitta A, Addie-Noye E, Tyler P, Quave CL. Anti-acne activity of Italian medicinal plants used for skin infection. Front Pharmacol 2016; 7: 425–438
- [263] Dulger B, Kilcik MA. Antifungal activity of *Ballota acetabulosa* against yeast *Candida* and *Cryptococcus* species. Asian J Chem 2011; 23: 413–415
- [264] Hashem M. Antifungal properties of crude extracts of five Egyptian medicinal plants against dermatophytes and emerging fungi. Mycopathologia 2011; 172: 37–46
- [265] Naz S, Farooq U, Khan A, Khan S, Sarwar R, Mirza N. Physicochemical screening and antimicrobial potential of *Otostegia limbata* Benth. J Chem Soc Pak 2014; 36: 683–686
- [266] Maqsood M, Qureshi R, Ikram M, Ali S, Rafi M, Khan JA, Ahmed MS. Preliminary screening of methanolic plant extracts against human rhabdomyosarcoma cell line from salt range, Pakistan. Pak J Bot 2015; 47: 353–357
- [267] Bahuguna RP, Jangwan JS, Singh R, Bhatt UP. *In vitro* cytotoxic, *in vitro* and *in vivo* antidiabetic activity of *Roylea cinerea*. Sci Revs Chem Commun 2015; 5: 69–76
- [268] Marimuthu N, Viswanathan T, Radha M, Suganya J. Computational screening of the phytochemicals from the plant *Ballota nigra* Linn against the human papillomavirus (HPV) E6. Res J Pharm Technol 2017; 10: 3095–3097
- [269] Fronza M, Murillo R, Ślusarczyk S, Adams M, Hamburger M, Heinzmann B, Laufer S, Merfort I. *In vitro* cytotoxic activity of abietane diterpenes from *Peltodon longipes* as well as *Salvia miltiorrhiza* and *Salvia sahendica*. Bioorg Med Chem 2011; 19: 4876–4881
- [270] da Cruz Araujo EC, Lima MAS, Montenegro RC, Nogueira M, Costa-Lotufu LV, Pessoa C, de Moraes MO, Silveira ER. Cytotoxic abietane diterpenes from *Hyptis martiusii* Benth. Z Naturforsch C Biosci 2006; 61: 177–183
- [271] Zhang Y, Ma R, Cheng S, Gu G. Marrubenol inhibits osteosarcoma cancer cell growth by inducing autophagic cell death and inhibiting cancer cell migration and invasion. J Balkan Union of Oncology 2018; 23: 729–734
- [272] Xiao CJ, Liu YC, Luo SH, Hua J, Liu Y, Li SH. Localisation of two bioactive labdane diterpenoids in the peltate glandular trichomes of *Leonurus japonicus* by laser microdissection coupled with UPLC-MS/MS. Phytochem Anal 2017; 28: 404–409
- [273] Ateyyat MA, Al-Mazra'awi M, Abu-Rjai T, Shatnawi MA. Aqueous extracts of some medicinal plants are as toxic as Imidacloprid to the sweet potato whitefly, *Bemisia tabaci*. J Insect Sci 2009; 9: 15
- [274] Al-Alawi MS. Acaricidal activity of medicinal plants against the developmental stage of the two spotted spider mite, *Tetranychus urticae* (Acari: Tetranychidae). Int J Agr Res 2014; 9: 38–46
- [275] Dube FF, Tadesse K, Birgersson G, Seyoum E, Tekie H, Ignell R, Hill SR. Fresh, dried or smoked? Repellent properties of volatiles emitted from ethnomedicinal plant leaves against malaria and yellow fever vectors in Ethiopia. Malar J 2011; 10: 375
- [276] Khan J, Anjum SI, Khan I, Rehman FU, Khan A. Larvicidal and development retarding effects of hexane crude extract of *Otostegia limbata* on 3rd instar larvae of *Drosophila melanogaster* Meign (Diptera: Drosophilidae). J Entomol Zool Stud 2015; 3: 6–9
- [277] Salari E, Ahmadi K, Zamani R. Study on the effects of acetonic extract of *Otostegia persica* (Labiatae) on three aphid species and one stored product pest. Adv Environ Biol 2010; 4: 346–349
- [278] Pascual-Villalobos MJ, Robledo A. Anti-insect activity of plant extracts from the wild flora in southeastern Spain. Biochem System Ecol 1999; 27: 1–10
- [279] Haq RU, Farooq U, Wahab A, Raza M, Ahmad VU, Khan RA. Investigation of antitussive and toxicological activity of *Ballota limbata* in mice. Pharm Biol 2011; 49: 627–632
- [280] Vural K, Ezer N, Erol K, Sahin FP. Anxiolytic and antidepressant activities of some *Ballota* species. J Fac Pharm Gazı 1996; 13: 29–32
- [281] Hajhashemi V, Rabbani M, Asghari GR, Karami-Saravi Z. Effects of *Otostegia persica* (Burm.f.) Boiss on morphine withdrawal syndrome in mice. Iranian J Pharm Res 2004; 3: 171–175
- [282] Ansari F, Shafaroodi H, Asgarpanah J. Anticonvulsant activity of *Otostegia persica* (Burm.) Boiss. Biosci Biotechnol Res Asia 2014; 11: 733–737
- [283] Çitoğlu GS, Özbek H, Sever B. Antinociceptive activity of *Ballota glandulosissima* Hub.-Mor & Patzak. Eastern J Med 2005; 10: 24–28
- [284] Nusier MK, Bataineh HN, Bataineh ZM, Daradka HM. Effects of *Ballota nigra* on glucose and insulin in alloxan-diabetic albino rats. Neuro Endocrinol Lett 2007; 28: 470–472

- [285] Nusier MK, Bataineh HN, Bataineh ZM, Daradka HM. Effects of *Ballota nigra* on blood biochemical parameters and insulin in albino rats. *Neuro Endocrinol Lett* 2007; 28: 473–476
- [286] Qazan WSh. Hypolipidaemic effects of *Ballota undulata* in rabbits. *Pak J Biol Sci* 2008; 11: 1169–1172
- [287] Ebrahimipoor MR, Khaksar Z, Noorafshan A. Anti-diabetic effect of orally administered *Otostegia persica* extract on streptozotocin diabetic rats. *Comp Clin Pathol* 2011; 20: 523–525
- [288] Manzari-Tavakoli A, Pouraboli I, Yaghoobi MM, Mehrabani M, Mirtadzadini SM. Antihyperglycemic, antilipid peroxidation, and insulin secretory activities of *Otostegia persica* shoot extract in streptozotocin-induced diabetic rats and *in vitro* C187 pancreatic  $\beta$ -cells. *Pharm Biol* 2013; 51: 253–259
- [289] Takhtfooladi MA, Asghari A, Hoseinzadeh HA, Mokhtari F. Effect of *Otostegia persica* extract on ischemia/reperfusion induced renal damage in diabetic rats. A biochemical study. *Acta Cir Bras* 2016; 31: 417–421
- [290] Akbarzadeh S, Bazzi P, Daneshi A, Nabipour I, Pourkhalili K, Mohebbi GH, Sartavi K, Abdi MR, Mirzaei M, Bargahi A. Anti-diabetic effect of *Otostegia persica* extract on diabetic rats. *J Med Plants Res* 2012; 6: 3176–3180
- [291] Ebrahimipoor-Mashhadi MR, Khaksar Z, Noorafshan A, Mogheisi B. Stereological study of the effects of orally administered *Otostegia persica* extract on pancreatic beta cells in male diabetic rats. *Comp Clin Pathol* 2014; 23: 761–767
- [292] Rezaian M, Shomali T, Dilmaghani A, Rassouli A. Ethanolic extract of *Otostegia persica* ameliorates bone loss in diabetic rats irrespective to its glucose lowering effect. *Comp Clin Pathol* 2014; 23: 1147–1151
- [293] Shewamene Z, Abdelwuhab M, Birhanu Z. Methanolic leaf extract of *Otostegia integrifolia* Benth reduces blood glucose levels in diabetic, glucose loaded and normal rodents. *BMC Complement Altern Med* 2015; 15: 19
- [294] Bhatt UP, Sati SC, Chandra S, Kumar S, Anthwal A, Singh R, Singh D, Kumar N, Kumar A, Bahuguna RP. Evaluation of *in vivo* and *in vitro* anti-diabetic activity of *Roylea cinerea*. *Int J Pharm Sci Rev Res* 2015; 32: 33
- [295] Suthar S, Patel R. The antihyperlipidaemic activity of aqueous *Leucas urticifolia* extract in Triton WR-1339 induced hyperlipidaemic rats. *Int J Pharm Technol* 2012; 4: 4314–4324
- [296] Qazan WSh. Effects of short and long term treatment of *Ballota undulata* on female albino rats fertility and pregnancy. *Pak J Biol Sci* 2008; 11: 638–642
- [297] Ganjali A, Sotoudeh A, Jahanshahi A, Takhtfooladi MA, Bazzazan A, Roodbari N, Harati MP. *Otostegia persica* extraction on healing process of burn wounds. *Acta Cir Bras* 2013; 28: 407–411
- [298] Takhtfooladi MA, Takhtfooladi HA, Moayer F, Karimi P, Asl HA. Effect of *Otostegia persica* extraction on renal injury induced by hindlimb ischemia-reperfusion: a rat model. *Int J Surg* 2015; 13: 124–130
- [299] Safaeian L, Ghasemi-Dehkordi N, Javanmard SH, Namvar H. Anti-hypertensive and antioxidant effects of a hydroalcoholic extract obtained from aerial parts of *Otostegia persica* (Burm.) Boiss. *Res Pharm Sci* 2015; 10: 192–199
- [300] Yeshanew S, Mekonnen Y. The effect of *Otostegia integrifolia* leaf extracts on the packed cell volume, body weight and survival time of *Plasmodium berghei* infected mice. *Int J Trop Med* 2013; 8: 129–134
- [301] Nateghpour M, Farivar L, Souri E, Hajjaran H, Mohebbali M, Haghi AM. The effect of *Otostegia persica* in combination with chloroquine on chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium berghei* using *in-vivo* fixed ratios method. *Iranian J Pharm Res* 2012; 11: 583–588
- [302] Dua VK, Verma G, Agarwal DD, Kaiser M, Brun R. Antiprotozoal activities of traditional medicinal plants from the Garhwal region of North West Himalaya, India. *J Ethnopharmacol* 2011; 136: 123–128
- [303] Bezenjani SN, Pouraboli I, Afshar RM, Mohammadi G. Hepatoprotective effect of *Otostegia persica* Boiss. shoot extract on carbon tetrachloride-induced acute liver damage in rats. *Iranian J Pharm Res* 2012; 11: 1235–1241
- [304] Akbartabar Toori M, Joodi B, Mehraban F, Mostafazadeh M, Ghavamizadeh M, Sadeghi H, Jafari M, Sadeghi H, Talebianpoor MS. Hepatoprotective activity of aerial parts of *Otostegia persica* against carbon tetrachloride-induced liver damage in rats. *Avicenna J Phyto-med* 2015; 5: 238–246
- [305] Upadhyay G, Malik J, Joshi R, Lakshmayya L, Singh UK. Hepatoprotective potential of lyophilized hydro-alcoholic extract of *Roylea elegans* Wall. against  $\text{CCl}_4$  and PCM induced hepatotoxicity in Wistar rats. *Ann Pharmacol Pharmaceut* 2017; 2: 1045
- [306] Hashemi F, Zarei MA. Tyrosinase inhibitory activity within hexane extract of ten screened plants from Kurdistan Province of Iran. *Int J Adv Biol Biomed Res* 2014; 2: 2795–2799
- [307] de Sales PM, de Souza PM, Simeoni LA, Magalhaes PDO, Silveira D.  $\alpha$ -Amylase inhibitors: a review of raw material and isolated compounds from plant source. *J Pharm Pharm Sci* 2012; 15: 141–183