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REVIEW ARTICLE

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Chemical profile of the Anatolian *Sideritis* species with bioactivity studies

Sema Çarıkçı[a], Turgut Kılıç[b], Ahmet C. Gören[c], Tuncay Dirmenci[d], Gülbahar Özge Alim Toraman[e] and Gülaçtı Topçu[e,f]

[a]Vocational School, Izmir Democracy University, Izmir, Turkey; [b]Department of Science Education, Necatibey Faculty of Education, Balıkesir University, Balıkesir, Turkey; [c]Department of Chemistry, Faculty of Basic Sciences, Gebze Technical University, Gebze, Turkey; [d]Department of Biology Education, Necatibey Faculty of Education, Balıkesir University, Balıkesir, Turkey; [e]Department of Pharmacognosy, Faculty of Pharmacy, Bezmialem Vakif University, Istanbul, Turkey; [f]Drug Application and Research Center (DARC), Bezmialem Vakif University, Istanbul, Turkey

ABSTRACT

Context: The genus *Sideritis* L. (Lamiaceae) is represented by 46 species in Turkey with an 79% endemism ratio, 42 of 46 belonging to the section Empodoclia.

Objective: In this review article, *Sideritis* species growing in Turkey have been evaluated for phytochemical constituents and biological activities.

Methods: The data for the isolates, components and extracts of the Anatolian *Sideritis* species and their bioactivity studies were retrieved from the main databases WoS, Scopus and PubMed from 1975 until 31 December 2022.

Results: In this review article, terpenoids, flavonoids, phenolics and other secondary metabolites isolated from Turkish *Sideritis* species were reported. Anatolian *Sideritis* species, which primarily consist of monoterpenes and sesquiterpenes, were studied in detail. *Sideritis* plants are represented by 46 species in Turkey, and 25 of them were investigated for their diterpenoids through isolation or LC–MS studies. Most of the diterpenoids of Turkish *Sideritis* species have *ent*-kaurene skeleton, among them linearol, siderol, 7-*epi*candicandiol and sideridiol were found to be the main compounds. Exceptionally, labdane, pimarane and beyerene diterpenoids were only found in a few species. For phenolics and flavonoids, only 12 species were investigated until now, and they were found to be rich in phenylethanoid glycosides and flavonoid glycosides. In terms of activity, most of the species were tested for antioxidant activity, followed by antimicrobial and anti-ulcer/anti-inflammatory activities. Their cytotoxic, enzyme inhibitory, antinociceptive and antistress activities were less frequently studied.

Conclusions: *Sideritis* species should be considered promising therapeutic agents in the treatment of upper respiratory tract and ulcer/inflammatory diseases.

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Introduction

The family Lamiaceae contains medicinal and aromatic plants, consisting of about 236 genera and 7000 species. The Lamiaceae family is spread over a wide area in a variety of habitats of Europe, Asia, Africa and Australia (Heywood 1996; Harley et al. 2004; Morales 2010). In Turkey, the Lamiaceae has 46 genera and approximately 600 taxa (Celep and Dirmenci 2017). In Turkey, *Salvia* L. and *Stachys* L. are the two Lamiaceae genera with a high number of species, and the other one, *Sideritis,* with a high endemism ratio (79%). The main distribution area of the *Sideritis* species is the Mediterranean basin; however, it has about 150 species and 42 hybrids, which spread from Bahamas and Canary Islands to China (WCVP 2023). Spain is the first country with 75 *Sideritis* species and Turkey is the second country in the world, both are the gene centres having maximum species of the genus (Morales 2000; Duman et al. 2005; Güvenç and Duman 2010; Selvi et al. 2022). The number of species in represented countries is as follows; Spain 75, Flora of Europe 28, Flora of U.S.S.R. 10, Greece 16, Bulgaria 5, Iran 4, Morocco 25, Italy 5, Syria, Palestine and Sinai 9 (Tutin et al. 1972; Shishkin and Yuzepchuk 1976; Papanikolou and Kokkini 1982; Pignatti 1982; Rechinger 1982; Feinbrun-Dothan 1986; Ghoumari et al. 2005; Dimopoulos et al. 2013; Aneva et al. 2022; Chrysargyris et al. 2023). In Turkey, *Sideritis* has a total of 46 species with about 79% endemism ratio (Huber-Morath and Davis 1982; Davis et al. 1988; Aytaç and Aksoy 2000; Guner et al. 2000; Celep and Dirmenci 2017).

The genus *Sideritis* is divided into two subgenera as subgenus *Marrubiastrum* (Moench) Mend.-Heuer. From the Macaronesian and subgenus *Sideritis* mainly distributed in the Mediterranean, the subgenus *Marrubiastrum* has 25 species and is divided into three sections: Sec. *Creticae* P. Perez et L. Negrın, Sect. *Empedocleopsis* Huynh and Sect. *Marrubiastrum* (Moench) Benth. The subgenus *Sideritis* has 125 species and is divided into four sections, which are two perennial (*Sideritis* and *Empedoclea* (Rafin) Benth. and two annual (*Hesiodia* (Moench) Benth. and *Burgsdorfia* (Moench) Briq.) sections (Barber et al. 2002).

While the annual species are included in *Hesiodia* (Moench) Benth. and *Burgsdorfia* (Moench) Briq sections, all of the

CONTACT Gülaçtı Topçu gtopcu@bezmialem.edu.tr; gulacti_topcu@yahoo.com Faculty of Pharmacy, Bezmialem Vakif University, P.O. Box 34093, Istanbul, Turkey

perennial species are included in *Empedoclea* (Rafin) Benth. (Duman et al. 2005; Güvenç and Duman 2010; Duman 2012), Turkey is one of the main gene centre of section *Empedoclia*.

There are several review studies on the genus *Sideritis* in the literature. While some of these studies reviewed the uses, chemical components and biological activities of a single *Sideritis* species (Todorova and Trendafilova 2014; Romanucci et al. 2017), other studies are in the form of various potential therapeutic properties (Todorova and Trendafilova 2014; Romanucci et al. 2017) or revisions of the chemical components and biological activities of these species (Gonzalez-Burgos et al. 2011; Fraga 2012; Aneva et al. 2019; Żyżelewicz et al. 2020).

A revision on *Sideritis* plants, reported by Gonzalez-Burgos et al. (2011), covers isolation studies besides some pharmacological activity studies including antimicrobial, anti-inflammatory and insecticidal activities of the isolated diterpenes and anti-HIV properties of some synthesized *ent*-kaurane diterpene derivatives.

Another revision study reported by Fraga (2012) concerned phytochemistry and chemotaxonomy of *Sideritis* species growing in the Mediterranean region, which were divided into four groups: species containing only triterpenes, but not diterpenes; containing bicyclic diterpenes in labdane type and not other diterpenes; containing *ent*-kaurene type skeleton with tetracyclic structure, and the last group diterpenes containing tetracyclic structures of the *ent*-beyer-15-ene and/or *ent*-atis-13-ene class.

Todorova and Trendafilova (2014) reported phytochemical studies, biological activity, cultivation, extraction and traditional uses of an important Balkan *Sideritis* species: *Sideritis scardica* Griseb. *Sideritis scardica* is an extremely popular and used herbal tea in Europe for the treatment of some diseases such as bronchitis and bronchial asthma; common cold, coughs and lung emphysema, in the treatment of inflammation, and gastrointestinal disorders, and used as an active constituent of dietary supplements for the prevention of anaemia. Other endemic *Sideritis* species of the Balkan Peninsula *Sideritis raeseri* Boiss. & Heldr. is also revised by Romanucci et al. (2017). This revision study has also reported that *S. raeseri* had effects on blood pressure and intestinal muscles, in addition to the similar biological properties listed for *S. scardica*.

Sideritis species have various pharmacological chemical groups like flavonoids and terpenoids, which have antimicrobial, anti-inflammatory, anti-ulcer, analgesic, antiviral, anti-tumour and antioxidant activities. In some diseases, their special uses are reported as review studies. While Abeshi et al. (2017) revised the potential of *Sideritis* species in ophthalmology, Uritu et al. (2018) reported the family of Lamiaceae species including *Sideritis* in pain therapy.

Sideritis species are a group of plants known as 'mountain tea' and 'valley tea' in Anatolia (local names are 'dağ çayı' or 'yayla çayı' in Turkish). Ethnobotanical studies have revealed that most commonly used plants in the Lamiaceae family are reported as *Sideritis* species with high endemism ratio in Turkey (Selvi et al. 2022). Some species are consumed as tea, flavouring agents and for medicinal purposes in several regions. Aerial parts of species have traditionally been used in the treatment of diseases such as stomatoid diseases, upper respiratory tract problems, wound treatment, diarrhoea, against colds and flu especially preparing their infusion in traditional medicine (Özcan et al. 2001; Selvi et al. 2022). The findings of anti-inflammatory, antimicrobial, antibacterial activity studies conducted on *Sideritis* species also support the traditional use of *Sideritis* taxa.

Even the tea of *Sideritis* species is served as sage (*Salvia*) in rural areas of Anatolia.

In the present study, we describe the chemical profile and bioactivity studies of *Sideritis* extracts and their isolates growing in Turkey reported from 1975 to December 2022. This is the first comprehensive review article on Turkish *Sideritis* species (see Table 1, Figure 1).

Phytochemistry of *Sideritis* species growing in Turkey

Lamiaceae family plants are well-known due to their terpenic constituents and flavonoids and other phenolics rather than other secondary metabolites. Most of the Lamiaceae plants are rich in their aromatic and volatile terpenes consisting of namely mono- and sesquiterpenes, which form their essential oils. However, the studies on the essential oils of *Sideritis* species mentioned that the yield is a low percentage.

Terpenoids

Monoterpenes and sesquiterpenes (essential oils)

Almost all members of Anatolian *Sideritis* species have been studied for their essential oil composition. For this purpose, gas chromatography (GC) and gas chromatography–mass spectrometry (GC–MS) were used, in general, and the oil was obtained by water distillation–hydrodistillation methods. Essential oils of Anatolian *Sideritis* species are rich in monoterpene hydrocarbons, and α-pinene, β-pinene, sabinene and myrcene are found in high amounts. Sesquiterpene hydrocarbon-rich species contain mainly β-caryophyllene, α-bisabolol, β-phellandrene, caryophyllene oxide and germacrene-D.

In Turkey, 42 of the total 46 *Sideritis* species grown belong to *Empedoclia* section except four annual ones (Baser 2002). The studies to determine of the components of the essential oils have been conducted by Kirimer et al. (1992, 1996, 2000, 2003, 2004), Kirimer, Tabanca, Ozek, et al. (1999), Kirimer, Tabanca, Tümen, et al. (1999), Kirimer, Tabanca, Demirci, et al. (2001) and Kirimer, Tabanca, Baser, et al. (2001). Essential oils of Turkish *Sideritis* species are classified into six groups, namely, 'monoterpene hydrocarbon-rich,' 'oxygenated monoterpene-rich,' 'sesquiterpene hydrocarbon-rich,' 'oxygenated sesquiterpene-rich,' 'diterpene-rich' and 'others'. Over half of the *Sideritis* species existing in Turkey belong to the 'monoterpene hydrocarbon-rich' group including also *S. brevidens* and *S. rubriflora* species (Kirimer, Tabanca, Ozek, et al. 1999; Kirimer et al. 2004). The studies (Baser 1993; Kirimer et al. 2004) pointed out a correlation between the oil yield and the main groups of constituents in the *Sideritis* essential oils indicated by Kirimer et al. (2004) 'The higher the oil yield, the higher the monoterpene hydrocarbon content, the lower the oil yield, the higher the sesquiterpene content'.

In a later study, two collected and cultivated *Sideritis* species; *S. congesta* and *S. condensata* were comparatively investigated for their essential oils (Gumuşçu et al. 2011). The essential oils ratio of the natural *S. congesta* species was found as 0.11% while in cultivated one was 0.12%. Natural and cultivated *S. condensata* essential oils ratio was found to be 0.008% and 0.01%, respectively. The main constituents of both natural and cultivated *S. congesta* essential oils were determined as β-pinene and α-pinene while in both essential oils of *S. condensata*, caryophyllene and germacrene were found as main components.

There is a taxonomic report based on chemical characters of *S. montana* L. subsp. *montana* and *S. vulcanica* (Karaborklu 2014).

During the period of 2004–2022, several essential oil studies on the Anatolian *Sideritis* species were carried out and detected

Table 1. Phytochemical constituents of Anatolian *Sideritis* species with bioactivities.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis akmanii Aytac, Ekici & Donmez (E)	Mono and sesquiterpenoids[a]	α-Curcumene	Kirimer et al. (2004)
		Spathulenol	
	Diterpenoids	Linearol	Bondi et al. (2000)
		Isolinearol	
		Foliol	
		Isofoliol	
		Sideridiol	
		Sideroxol	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Aksoy et al. (2022)
		Anticholinesterase	
		Alpha-amylase	
		Alpha-glucosidase	
		ACE inhibitory activities	
Sideritis albiflora Hub.-Mor.(E)	Mono and sesquiterpenoids[a]	α-Pinene	Kirimer et al. (2004)
		β-Pinene	Topcu et al. (2005)
		trans-Caryophyllene	Kirci et al. (2021)
		β-Caryophyllene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antimicrobial	Dulger, Gonuz, et al. (2005) and Dulger, Ugurlu, et al. (2005)
		Antioxidant	
		Antidiabetic	Güvenç et al. (2005)
			Deveci et al. (2020)
Sideritis amasiaca Bornm. (E)	Mono and sesquiterpenoids[a]	α-Pinene	Kirimer et al. (2004)
		β-Pinene	Tumen et al. (1995)
		Bicyclogermacrene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)
Sideritis arguta Boiss. & Heldr. (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene	Kirimer et al. (2004)
		β-Phellandrene	Baser, Kirimer, et al. (1996)
		Germacrene D	
		β-Pinene	
		α-Pinene	
		1,8-Cineole	
	Diterpenoids	7-*epi*-Candicandiol	Ertaş et al. (2009)
		Siderol	
		Sideroxol	
		Eubotriol	
		Diacetyl-distanol	
		15-*epi*-Eubol	
		Eubol	
		Epoxy-siderol	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
		Anti-inflammatory	Erdogan-Orhan et al. (2010)
		Anticholinesterase	Erkan et al. (2011)
			Yeşlada and Ezer (1989)
			Ertaş et al. (2009)
Sideritis argyrea P. H. Davis (E)	Mono and sesquiterpenoids[a]	β-Phellandrene	Ezer et al. (1996)
		β-Pinene	Kirimer et al. (2003)
		α-Pinene	Kirimer et al. (2004)
		Limonene	
	Diterpenoids	Linearol	Kilic et al. (2003)
		Foliol	
		Sidol	
		7-*epi*-Candicandiol	
		7-*epi*-Candicandiol-18-monoacetate	
		Siderol	
		Sideridiol	
		Ent-7α-acetoxy-18-hydroxy-kaur-16-ene	
		Ent-6β,8α-dihydroxy-labd-13(16),14-diene[b]	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Anti-inflammatory	Yeşilada and Ezer (1989)
		Antioxidant	Tunalier et al. (2004)
		Antibacterial	Kilic et al. (2003)
Sideritis armeniaca Bornm. (E)	Mono and sesquiterpenoids[a]	β-Phellandrene	Kirimer et al. (2003)
		α-Pinene	Kirimer et al. (2004)
		β-Pinene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis athoa Papanikolaou & Kokkini	Mono and sesquiterpenoids[a]	Myrcene	Ozek et al. (1993)
		β-Pinene	
		Ar-Curcumene	
	Diterpenoids	Linearol	Kilic et al. (2003)
		Foliol	Topcu et al. (1999)
		Sidol	
		Ent-3β,7α-dihydroxy-kaur-16-ene	
		7-*epi*-Candicandiol	
		Ent-3β-hydroxy-kaur-16-ene	
		Athonolone	
		Ent-3α,18-dihydroxy-kaur-16-ene	
		Ent-7α,18-dihydroxy-beyer-15-ene[c]	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antistress	Öztürk et al. (1996)
		Antibacterial	Kilic et al. (2003)
		Antioxidant and anticholinesterase	Carikci (2020)
Sideritis bilgerana P. H. Davis (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	Iscan et al. (2005)
		Limonene	Özcan et al. (2001)
		β-Phellandrene	Carikci et al. (2018)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	*Candida albicans* inhibitory	Dulger et al. (2006)
		Antioxidant	Tunalier et al. (2004)
		Antimicrobial	Tekeli (2012)
			Iscan et al. (2005)
Sideritis brevibracteata P. H. Davis (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene, naphthalene	Kırımer et al. (2004)
		Caryophyllene	Sagir et al. (2017)
		Germacrene-D	Carikci et al. (2018)
		α-Cadinene	
	Diterpenoids	Siderol (*ent*-7α-acetyl-18-hydroxy-kaur-15-ene)	Sagir et al. (2017)
		Linearol (*ent*-3β,7α-dihydroxy-18-acetoxykaur-16-ene)	
		Eubotriol (*ent*-7α,15β,18-trihydroxy-kaur-16-ene)	
		Sideridiol (*ent*-7α,18β-dihydroxy-kaur-15-ene)	
		Athonolone (*ent*-7α,17,18-trihydroxy-9,11-(ene)-12-on)	
	Triterpenoids and steroids	Stigmasterol	
	Phenolics, flavonoids and derivatives	Hypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside	Tandogan et al. (2011) Güvenç et al. (2010)
		Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside	
		Hypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside	
		Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside	
		3′-Hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-*g*lucopyranoside	
		Hypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside	
		Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside	
		3′-Hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside	
		Hypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6‴-*O*-acetyl-β-$_D$ glucopyranoside	
		Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6‴-*O*-acetyl-β-D-glucopyranoside	
		3′-Hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside	
	Phenylethanoid glycoside	Verbascoside	Güvenç et al. (2010)
	Activity	Anti-inflammatory, antinociceptive, antioxidant and aldose reductase inhibitory	Güvenç et al. (2010) Güvenç et al. (2005)
		Antioxidant	Dulger, Gonuz, et al. (2005) and
		Antimicrobial	Dulger, Ugurlu, et al. (2005)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis brevidens P. H. Davis (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	Kirimer, Tabanca, Ozek, et al. (1999)
		epi-Cubebol	
	Diterpenoids	Linearol	Bondi et al. (2000)
		Sidol	Carikci et al. (2012)
		epi-Candicandiol	
		Siderol	
		Athonolone	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antimicrobial	Dulger, Gonuz, et al. (2005) and Dulger, Ugurlu, et al. (2005)
		Antioxidant	Tunalier et al. (2004)
			Carikci et al. (2012)
Sideritis caesarea H. Duman, Aytac & Baser (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene	Kirimer et al. (2004)
		α-Pinene	Kirimer, Tabanca, Tümen, et al. (1999)
		β-Pinene	Gunbatan et al. (2017)
	Diterpenoids	Siderol	Baser, Bondi, et al. (1996) and Baser, Kirimer, et al. (1996)
		Epoxy-siderol	Halfon et al. (2011)
		Eubol	
		Eubotriol	
		ent-7*α*,18-Dihydroxy-15-oxokaur-16-ene	
	Phenolics, flavonoids and derivatives	Penduletin	Demirtas et al. (2011)
		Apigenin	
		4′-*O*-Methylisoscutellarein-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-Acetyl-β-D-glucopyranoside	
		4′-*O*-Methylhypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-Acetyl-β-D-glucopyranoside	
		Isoscutellarein-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-Acetyl-β-D-glucopyranoside	
		Isoscutellarein-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside	
		4′-*O*-Methylhypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-Glucopyranoside	
		Hypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside	
	Activity	Anticholinesterase	Halfon et al. (2013)
		Antioxidant	Tunalier et al. (2004)
		Antioxidant and antimicrobial	Sagdic et al. (2008)
		Antifungal	Askun et al. (2008)
		Anti-ulcerogenic	Güvenç et al. (2005)
Sideritis cilicica Boiss. & Bal. (E)	Mono and sesquiterpenoids[a]	α-Pinene	Kirimer et al. (2004)
		β-Pinene	
		β-Phellandrene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antimicrobial	Iscan et al. (2005)
		Antioxidant	Dulger, Gonuz, et al. (2005) and Dulger, Ugurlu, et al. (2005)
			Tunalıer et al. (2004)
Sideritis condensata Boiss. & Heldr. apud Benth. (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene	Kirimer et al. (2004)
		Hexahydrofarnesyl acetone	Ozkan et al. (2005)
		Germacrene D	Ezer et al. (1996)
		Carvacrol	Gumuşçu et al. (2011)
		β-Pinene	
		α-Pinene	
		β-Caryophyllene	
	Diterpenoids	Linearol	Kilic et al. (2009)
		Isolinearol	
		Siderol	
		Sideridiol	
		Candol B	
		Sideroxol	
		7-Acetyl-sideroxol	
		Ent-7α-acetoxy-15β,18-dihydroxy-kaur-16-ene	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
		Insecticidal	Kara et al. (2014)
		Antioxidant and antimicrobial	Kilic et al. (2009)
		Candida albicans inhibitory	Ozkan et al. (2005)
			Dulger et al. (2006)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis congesta P. H. Davis & Hub.-Mor. (E)	Mono and sesquiterpenoids[a]	*epi*-Cubebol	Kirimer, Tabanca, Baser, et al. (2001)
		δ-Cadinene	Ozel et al. (2008)
		α-Cadinol	Kirimer et al. (2004)
		β-Pinene	Ezer et al. (1996)
		α-Pinene	Gumuşçu et al. (2011)
		Caryophyllene	Özcan et al. (2001)
		Muurol-5-en-4-β-ol	
		Muurol-5-en-4-α-ol	
		α-Cadinol	
	Iridoid glycoside	Ajugoside	Bardakci et al. (2020)
	Diterpenoids	Linearol	Topcu et al. (2011)
		Epoxy-isolinearol	
		Sidol	
		7-*epi*-Candicandiol	
		Siderol	
		Sideridiol	
		Sideroxol	
		7-Acetyl-distanol	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Analgesic activity	Aydın et al. (1996)
		Antioxidant	Güvenç et al. (2005)
		Anti-inflammatory	Erdogan-Orhan et al. (2010)
			Erkan et al. (2011)
			Yeşlada and Ezer (1989)
Sideritis curvidens Stapf	Mono and sesquiterpenoids[a]	Bicyclogermacrene	Kirimer et al. (2000)
		β-Caryophyllene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antibacterial	Uğur et al. (2005)
Sideritis cypria Post	Mono and sesquiterpenoids[a]	*epi*-Cubebol	Yiğit Hanoğlu et al. (2017)
		trans-Piperitol	
		Pinene	
	Iridoid glycoside	7-*O*-Acetyl-8-epi-loganic acid	Hanoğlu et al. (2019)
	Diterpenoids	Sidol	Hanoğlu et al. (2019)
		Isosidol	
		Linearol	
		Isolinearol	
	Phenolics, flavonoids and derivatives	Apigenin-7-*O*-glucopyranoside	Hanoğlu et al. (2019)
		Isoscutellarein-7-*O*-[6‴-*O*-acetyl-allopyranosyl-(1→2)-glucopyranoside],	
		mixture of apigenin-7-*O*-(4″-*O*-p-coumaroyl)-glucopyranoside and apigenin-7-*O*-(3″-*O*-p-coumaroyl)-glucopyranoside	
	Phenylethanoid glycoside	Verbascoside	Hanoğlu et al. (2019)
		Lavandulifolioside	
		Leonoside A	
		Leucoseptoside A	
	Activity	Antimicrobial activity of essential oil	Yiğit Hanoğlu et al. (2017)
Sideritis dichotoma Huter (E)	Mono and sesquiterpenoids[a]	Geracymene	Kirimer et al. (2004)
		Hexahydrofarnesyl-acetone	
	Diterpenoids	Geraterpinene	Kirimer et al. (2004)
		Siderol	Topcu et al. (2002b)
		Sideridiol	
		Sideroxol	
		Epoxy-siderol	
		Eubotriol	
		ent-7α-Acetoxy-15β,18-dihydroxy-kaur-16-ene	
		ent-7α,18-Dihydroxy-beyer-15-ene[c]	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
		Candida albicans inhibitory	Tunalier et al. (2004)
		Antibacterial	Dorman et al. (2011)
			Dulger et al. (2006)
			Diken and Yılmaz (2022)
Sideritis erythrantha Boiss. & Heldr. apus Benth. var. *erythrantha* Boiss. & Heldr. apud Benth. (E)	Mono and sesquiterpenoids[a]	Myrcene	Kirimer et al. (2004)
		α-Pinene	Tabanca et al. (2001)
		β-Phellandrene	Altundag and Aslim (2011)
		β-Caryophyllene	
		β-Pinene	
		Sabinene	
	Diterpenoids	Sideridiol	Bruno et al. (2005)
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antimicrobial activity	Köse et al. (2010)
		Antioxidant	Altundag and Aslim (2011)
		Antioxidant and antimicrobial	Güvenç et al. (2005)
			Tunalier et al. (2004)
			Ozkan et al. (2005)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis erythrantha Boiss. & Heldr. apud Benth. var. *cedretorum* P. H. Davis (E)	Mono and sesquiterpenoids[a]	Myrcene	Kirimer et al. (2004)
		α-Pinene	Köse et al. (2010)
		α-Bisabolol	Tabanca et al. (2001)
		β-Caryophyllene	
		β-Pinene	
		Sabinene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antimicrobial activity	Köse et al. (2010)
		Antioxidant	Tunalier et al. (2004)
			Güvenç et al. (2005)
			Dorman et al. (2011)
Sideritis galatica Bornm. (E)	Mono and sesquiterpenoids[a]	Germacrene-D	Kirimer et al. (2004)
		α-Pinene	Zengin et al. (2016)
		β-Pinene	
		β-Caryophyllene	
	Diterpenoids	Galaticat[b]	Dişli et al. (2002)
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant and enzyme inhibitory	Zengin et al. (2014)
		Antioxidant	Tunalier et al. (2004)
		Antimicrobial	Tosun et al. (2006)
		Candida albicans inhibitory	Dulger et al. (2006)
		Antioxidant and enzyme inhibitory activities of essential oil	Zengin et al. (2016)
Sideritis germanicopolitana Bornm.	Mono and sesquiterpenoids[a]	N.W.	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	Xanthomicrol	Kirmizibekmez et al. (2021)
		Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allo pyranosyl-(1→2)]-β-glucopyranoside	Adem et al. (2019)
		4′-*O*-Methyl isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allo pyranosyl-(1→2)]-β-glucopyranoside	
		3′-Hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside	
		Dehydrodiconiferyl alcohol 4-*O*-β-D-glucopyranose	
		Pinoresinol 4′-*O*-β-glucopyranoside	
	Phenylethanoid glycoside	Verbascoside	Kirmizibekmez et al. (2021)
		Martynoside	
		Leucoseptoside A	
		Decaffeoyl verbascoside	
		Lamalboside	
	Iridoid Glycosides	Melittoside	Kirmizibekmez et al. (2021)
		5-Allosyloxy-aucubine	
		Ajugol	
	Activity	N.W.	
Sideritis germanicopolitana subsp. *germanicopolitana* Bornm. (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		Myrcene	Kirimer et al. (1992)
		α-Pinene	
		Sabinene	
		Elemol	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)
Sideritis germanicopolitana subsp. *viridis* Hausskn. ex Bornm. (E)	Mono and sesquiterpenoids[a]	Myrcene	Kirimer et al. (2004)
		α-Pinene	Kirimer et al. (1992)
		β-Pinene	Bayan and Aksit (2016)
		Sabinene	
		Elemol	
		α-Pinene	
		α-Limonene	
		β-Pinene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antifungal activity of the oil and methanol extract	Bayan and Aksit (2016)
		Antioxidant	Tunalier et al. (2004)
Sideritis gulendamiae H. Duman & Karaveliogullari (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	
	Diterpenoids	Linearol	Bondi et al. (2000)
		7-*epi*-Candicandiol	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)
Sideritis hispida P. H. Davis (E)	Mono and sesquiterpenoids	β-Pinene	Kirimer et al. (2004)
		α-Pinene	Sarikaya and Canis (2019)
		Limonene	Carikci et al. (2018)
		Myrcene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	N.W.	

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis hololeuca Boiss. & Heldr. apud Benth. (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	Kirimer et al. (2004)
		β-Phellandrene	Kirimer et al. (2003)
		3-Methylnonane	Carikci et al. (2020)
		Aromadendrene	
	Diterpenoids	Linearol	Carikci et al. (2020)
		Siderol	
		7-Acetoxy sideroxol	
		Eubol	
		Eubotriol	
		7-*epi*-Candicandiol	
		ent-7α-Acetoxy-18-hydroxykaur-16-ene	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)
		Anticholinesterase	Carikci et al. (2020)
			Carikci et al. (2020)
Sideritis huber-morathii Greuter & Burdet (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	
	Diterpenoids	Linearol	Baser, Bondi, et al. (1996)
		Sidol	
		Candicandiol	
		Siderol	
		Sideridiol	
		3,7,18-Triacetyl-foliol	
		Foliol-3,18-acetonide	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)
			Güvenç et al. (2005)
Sideritis lanata L.	Mono and sesquiterpenoids[a]	Spathulenol	Kirimer et al. (2000)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antistress	Öztürk et al. (1996)
		Antibacterial activity of the essential oils	Uğur et al. (2005)
Sideritis leptoclada O. Schwarz & P. H. Davis (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene	Kirimer et al. (2004)
		Germacrene-D	
	Diterpenoids	Linearol	Kilic et al. (2005)
		Sidol	
		7-*epi*-Candicandiol	
		Eubotriol	
		Sideroxol	
		18-Acetyl-sideroxol	
		7-Acetyl-sideroxol	
		Ent-7α-acetoxy-15β,18-dihydroxy-kaur-16-ene	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
		Cytotoxic activity	Ayar-Kayalı et al. (2009)
		Antidiabetic	Aydoğmuş-Öztürk et al. (2018)
			Deveci et al. (2020)
Sideritis libanotica Labill. ssp. *kurdica* (Bornm.) Hub.-Mor.	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antistress	Öztürk et al. (1996)
		Antioxidant	Tunalıer et al. (2004)
Sideritis libanotica ssp. *libanotica*	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	
	Diterpenoids	Siderol	Bruno et al. (2005)
		Sideridiol	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
		Anticholinesterase	Korkmaz et al. (2017)
Sideritis libanotica ssp. *linearis* (Bentham) Bornm. (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		β-Caryophyllene	Schulz et al. (2005)
		Hexadecanoic acid	
		α-Pinene	
	Diterpenoids	Sideridiol	Demirtas et al. (2011)
	Phenolics, flavonoids and derivatives	3′-*O*-Methylhypolaetin	Demirtas et al. (2011)
		7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-Acetyl-β-D-glucopyranoside	Adem et al. (2019)
		3′-*O*-Methylhypolaetin-7-*O*-[6‴-*O*-acetyl-allosyl-(1→2)-6‴-*O*-acetyl-glycoside	
	Activity	Antioxidant	Demirtas et al. (2011)
		Antiproliferative	Tunalier et al. (2004)
		Antiinflammatory	Erdogan-Orhan et al. (2010)
		Enzyme activity	Tepe et al. (2006)
			Demirtaş et al. (2011)
			Yeşilada and Ezer (1989)
			Adem et al. (2019)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis libanotica subsp. *microchlamys* (Hand.-Mazz.) Hub.-Mor.	Mono and sesquiterpenoids[a]	β-Caryophyllene	Kirimer et al. (2004)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	N.W.	
Sideritis libanotica ssp. *violascens* (P. H. Davis) P. H. Davis (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene	Kirimer et al. (2004)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	N.W.	
Sideritis lycia Boiss. & Heldr. apud Benth. (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	Baser, Bondi, et al. (1996) and Baser, Kirimer, et al. (1996)
		Valeranone	
		1,8-Cineole	
	Diterpenoids	Linearol	Kilic et al. (2020)
		Sidol	
		7-*epi*-Candicandiol	
		Foliol	
		Isolinearol	
		Isosidol	
		Siderol	
		Sideridiol	
	Phenolics, flavonoids and derivatives	N.W.	
	Phenylethanoid glycoside	Verbascoside (acteoside)	Akcos et al. (1999)
		Martynoside	
		Leucosceptoside A	
		Lavandulifolioside	
	Activity	Antiinflammatory	Akcos et al. (1999)
		Cytotoxic and antiviral	Kilic et al. (2020)
Sideritis montana L. ssp. *montana*	Mono and sesquiterpenoids[a]	Bicyclogermacrene	Kirimer et al. (2000)
		Germacrene-D	Kilic (2014)
		β-Caryophyllene	
		α-Pinene	
		β-Pinene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant and antimicrobial	Emre et al. (2011)
		Antifungal	Balkan et al. (2019)
Sideritis montana subsp. *remota* (d'URV.) P. W. Ball ex Heywood	Mono and sesquiterpenoids[a]	Bicyclogermacrene	Kirimer et al. (2000)
		Germacrene-D	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	N.W.	
Sideritis niveotomentosa Hub.-Mor. (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene	Kirimer et al. (2004)
	Diterpenoids	Linearol	Bondi et al. (2000)
		Foliol	Carikci et al. (2012)
		7-*epi*-Candicandiol	
		Siderol	
		Sideridiol	
		Sidol	
		Eubotriol	
		Eubol	
		Athonolone	
		7-*epi*-Candicandiol	
	Phenolics, flavonoids and derivatives	Cirsimaritin (5,4′-dihydroxy-6,7-dimethoxyflavone)	Bondi et al. (2000)
	Activity	Antioxidant	Tunalier et al. (2004)
			Carikci et al. (2012)
Sideritis ozturkii Aytac & Aksoy (E)	Mono and sesquiterpenoids[a]	Bicyclogermacrene	Kirimer, Tabanca, Demirci, et al. (2001)
		β-Pinene	
		α-Pinene	Kirimer et al. (2004)
	Diterpenoids	Linearol	Sahin et al. (2004)
		Epoxy-isolinearol	
		Sidol	
		7-*epi*-Candicandiol	
		Sideroxol	
	Phenolics, flavonoids and derivatives	Chrysoeriol 7-*O*-[2‴-*O*-caffeoyl-6‴-*O*-acetyl-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside]	Sahin et al. (2004)
		Chrysoeriol 7-*O*-[2‴-*O*-caffeoyl-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside]	
		Chrysoeriol 7-*O*-[2‴-*O*-p-coumaroyl-6‴-β-*O*-acetyl-D-glucopyranosyl-(1→2)-β-D-glucopyranoside]	
	Phenylethanoid glycoside	Leucoseptoside A	Sahin et al. (2004)
		Martynoside	
		Verbascoside	
	Activity	Antioxidant and antimicrobial	Sagdic et al. (2008)
		Antiinflammatory and antinociceptive	Küpeli, Sahin, Caliş, et al. (2007) and Küpeli, Sahin, Yeşilada, et al. (2007)
		Antioxidant	Tunalıer et al. (2004)
		Antioxidant and enzyme inhibitory	Zengin et al. (2019)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis perfoliata L.	Mono and sesquiterpenoids[a]	8α,13-Hydroxy-14-en-*epi*-labdane	Kirimer et al. (2004)
		Limonene	Ozkan et al. (2005)
		Viridiflorol	Karaborklu (2014)
		α-Bisabolol	Ezer et al. (1996)
		β-Caryophyllene	
		Myrcene	
		Germacrene-D	
		α-Pinene	
		β-Pinene	
		β-Phellandrene	
		Limonene	
		α-Pinene	
		β-Pinene	
	Diterpenoids	*Ent*-2α-hydroxy-13-*epi*-manoyl oxide[b]	Sezik et al. (1985)
		Siderol	Bruno et al. (2005)
		Sideridiol	
		Sideritriol	
	Phenolics, flavonoids and derivatives	4′-O-Methyl-isoscutellarein-7-*O*-(2″-*O*-6-*O*-acetyl-β-D-allopyranosyl)-β-D-glucopyranoside	Ezer et al. (1992)
		3′-Hydroxy-4′-*O*-methyl-isoscutellarein-7-*O*-(2″-*O*-6‴*O*-acetyl-β-D-allopyranosy1)-β-D-glucopyranoside	
		Apigenin-7-*O*-(4″-*O*-p-coumaroyl)-β-D-glucopyranoside	
	Phenylethanoid glycoside	Acteoside	Ezer et al. (1992)
	Activity	Antioxidant	Erdogan-Orhan et al. (2010)
		Antistress	Öztürk et al. (1996)
		Antiinflammatory	Yeşlada and Ezer (1989)
		Enzyme inhibitory activities	Sarikurkcu et al. (2019)
Sideritis phlomoides Boiss. & Bal. (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer, Tabanca, Tümen, et al. (1999)
		α-Pinene	
		β-Caryophyllene	Kirimer et al. (2004)
		Caryophyllene oxide	
		α-Bisabolol	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)
Sideritis phrygia Bornm. (E)	Mono and sesquiterpenoids[a]	β-Pinene	Kirimer et al. (2004)
		α-Pinene	Carikci et al. (2018)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalier et al. (2004)
			Güvenç et al. (2005)
			Tekeli (2012)
Sideritis pisidica Boiss. & Heldr. apud Benth. (E)	Mono and sesquiterpenoids[a]	Myrcene	Kirimer et al. (2004)
		β-Caryophyllene	Ozkan et al. (2005)
		α-Bisabolol	Ergun et al. (2016)
		Sabinene	Deveci et al. (2017)
		α-Pinene	Carikci et al. (2018)
		α-Pinene	Arslan et al. (2021)
		Sabinene	
		β-Caryophyllene	
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
		Antimicrobial	Erdogan-Orhan et al. (2010)
		Antiinflammatory	Dulger, Gonuz, et al. (2005) and Dulger, Ugurlu, et al. (2005)
		Antidiabetic	Yeşlada and Ezer (1989)
			Deveci et al. (2020)
Sideritis romana L. ssp. *romana* L. (E)	Mono and sesquiterpenoids[a]	Thymol	Kirimer et al. (2000)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	N.W.	
Sideritis rubriflora Hub.-Mor. (E)	Mono and sesquiterpenoids[a]	*epi*-Cubebol	Kirimer, Tabanca, Ozek, et al. (1999)
		β-Pinene	
		α-Pinene	Kirimer et al. (2004)
		Germacrene-D	Chalchat et al. (2011)
	Diterpenoids	Linearol	Bondi et al. (2000)
		Sidol	
		7-*epi*-Candicandiol	
		Sideroxol	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	*Candida albicans* inhibitory	Dulger et al. (2006)
		Antioxidant	Tunalier et al. (2004)
			Güvenç et al. (2005)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis scardica Griseb subsp. *scardica*	Mono and sesquiterpenoids[a]	β-Pinene β-Caryophyllene Carvacrol α-Pinene β-Pinene Carvacrol	Kirimer et al. (2004) Baser et al. (1997)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	N.W.	
Sideritis serratifolia Hub.-Mor. (E)	Mono and sesquiterpenoids[a]	Calamenene	Kirimer et al. (2004)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant activity	Tunalier et al. (2004) Güvenç et al. (2005)
Sideritis sipylea Boiss.	Mono and sesquiterpenoids[a]	α-Pinene β-Pinene Myrcene	Kirimer et al. (2004)
	Diterpenoids	Linearol Siderol 7-*epi*-Candicandiol Linearol Isolinearol Epoxy-isolinearol Isosidol 7-*epi*-Candicandiol Siderol Sideridiol	Loğoğlu et al. (2006) Topcu et al. (2002b)
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	*Candida albicans* inhibitory Antioxidant	Dulger et al. (2006) Güvenç et al. (2005) Nakiboglu et al. (2007)
Sideritis stricta Boiss. & Heldr. apud Benth. (E)	Mono and sesquiterpenoids[a]	β-Pinene α-Pinene β-Caryophyllene	Kirimer et al. (2004) Kirimer et al. (2003)
	Diterpenoids	Sideridiol Isosidol Isolinearol Linearol *ent*-1β-Hydroxy-7α-acetyl-15β,16β-epoxykaurane Sideroxol 7-Acetylsideroxol 7-*epi*-Candicandiol Eubotriol Eubol Foliol Sideridiol Siderol	Şahin et al. (2006) Kilic (2006)
	Phenolics, flavonoids and derivatives	Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside Xanthomicrol	Şahin et al. (2006)
	Phenylethanoid glycoside	Verbascoside	Şahin et al. (2006)
	Activity	Antiinflammatory and antinociceptive Cytotoxic and membrane damaging effects Antidiabetic	Küpeli, Sahin, Yeşilada, et al. (2007) Erdoğan et al. (2018) Deveci et al. (2020)
Sideritis syriaca L. ssp. *nusairiensis* (Post) Hub.-Mor.	Mono and sesquiterpenoids[a]	β-Pinene α-Pinene	Kirimer et al. (2004)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
Sideritis taurica Stephan ex Willd.	Mono and sesquiterpenoids[a]	Germacrene D α-Bisabolol β-Pinene α-Pinene β-Caryophyllene	Kirimer et al. (2004) Kirimer et al. (2003)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant Antimicrobial and antitumour	Tunalier et al. (2004) Turker et al. (2018)

(*Continued*)

Table 1. Continued.

Species	Isolated compounds, and main chemical components of the essential oils[a]		References
Sideritis tmolea P. H. Davis (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene α-Cadinol β-Caryophyllene Calamenene	Kirimer et al. (2004) Özcan et al. (2001)
	Diterpenoids	Athonolone Siderol Eubotriol Diacetyl-distanol 7-Acetyl-sideroxol	Carikci et al. (2007)
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Güvenç et al. (2005)
Sideritis trojana Bornm. (E)	Mono and/or sesquiterpenoids[a]	β-Pinene α-Pinene	Kirimer et al. (2004) Kirmizibekmez et al. (2017) Paşa et al. (2019)
	Iridoid glycosides	Melittoside 10-*O*-(*E*)-Feruloylmelittoside 10-*O*-(*E*)-*p*-Coumaroylmelittoside Stachysoside E Stachysoside G	Kirmizibekmez et al. (2012)
	Diterpenoids	7-*epi*-Candicandiol Siderol Sideridiol Isocandol B Candol A acetate *ent*-7α-Acetoxy-kaur-15-ene 7-Acetyl-sideroxol *ent*-2α-Hydroxy-8(14),15-pimaradiene[d]	Topcu et al. (2002a)
	Phenolics, flavonoids and derivatives	di-*O*-Methylcrenatin Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside, 4′-O-Methyl-isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside, 3′-Hydroxy-4′-*O*-methyl-Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside	Kirmizibekmez et al. (2012)
	Phenylethanoid glycosides	Verbascoside Isoacteoside Lamalboside Leonoside A Isolavandulifolioside	Kirmizibekmez et al. (2012)
	Activity	*Candida albicans* inhibitory Insecticidal	Dulger et al. (2006) Aslan et al. (2006)
Sideritis vulcanica Hub.-Mor. (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene Germacrene-D Caryophyllene oxide β-Pinene α-Pinene Germacrene D	Kirimer, Tabanca, Tümen, et al. (1999) Kirimer et al. (2004)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant	Tunalıer et al. (2004)
Sideritis vuralii H. Duman & Baser (E)	Mono and sesquiterpenoids[a]	β-Caryophyllene Caryophyllene oxide Spathulenol β-Pinene α-Pinene β-Phellandrene	Kirimer, Tabanca, Tümen, et al. (1999) Kirimer et al. (2004)
	Diterpenoids	N.W.	
	Phenolics, flavonoids and derivatives	N.W.	
	Activity	Antioxidant Antifungal Antimicrobial	Tunalıer et al. (2004) Dorman et al. (2011) Askun et al. (2008) Dulger, Ugurlu, et al. (2005)

N.W.: no work reported; (E): endemic.
[a]Mono and sesquiterpenoids
[b]Labdane diterpene.
[c]Beyerane diterpene.
[d]Pimarane diterpene.

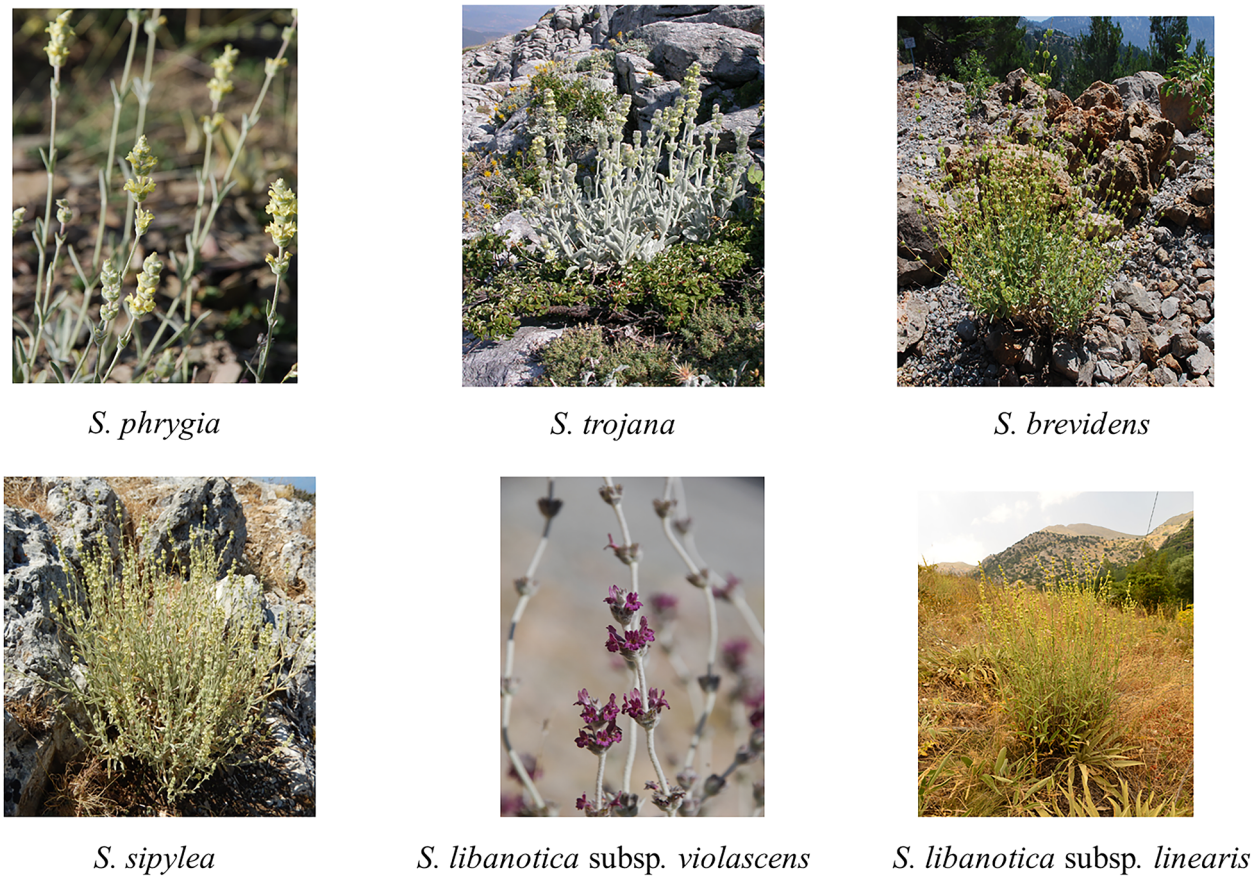


Figure 1. Some Anatolian *Sideritis* species.

by GC or GC–MS, or in some cases, detected by using direct thermal desorption and headspace GC–MS techniques (Topcu et al. 2005; Ozel et al.2008)

The biological activity of the investigated Anatolian *Sideritis* extracts and the main chemical components of the essential oils are given in Table 1. However, biological activity results of the isolated diterpenoids, mainly kaurenoids, are given in the text.

Iridoid glycosides

Chemical profile of the methanol extract of *S. trojana* was studied by Kirmizibekmez et al. (2012) and found five known iridoid glycosides (melittoside, 10-*O*-(E)-feruloylmelittoside, 10-*O*-(E), *p*-coumaroylmelittoside, stachysoside E and stachysoside G).

In another study, three iridoid glycosides (melittoside, 5-allosyloxy-aucubine, ajugol) were isolated from *S. germanicopolitana* methanol extract by Kirmizibekmez et al. (2021).

The chromatographic separations on the aqueous fraction from *S. congesta* afforded an iridoid glycoside, ajugoside (Bardakci et al. 2020).

n-BuOH extract of *S. cypria* was submitted to reverse phase vacuum liquid chromatography and afforded an iridoid glycoside, 7-*O*-acetyl-8-*epi*-loganic acid, which was reported for the first time for the genus *Sideritis* (Hanoğlu et al. 2019).

On the other hand, Lytra et al. (2021) investigated aerial parts of the cultivated *S. cypria* methanol extract and isolated two iridoids (melittoside and 8-*epi*-loganic acid) and three *ent*-kaurane diterpenoids. The same extract was also afforded three phenolic glycosides, six phenylethanoid glycosides and seven flavone derivatives (Lytra et al. 2021). This cultivated plant was further investigated for its flowers on the prepared water extract (infusion), which afforded an iridoid glycoside (melittoside), one phenolic acid (chlorogenic acid), four phenylethanoid glycosides and four flavones (Lytra et al. 2020).

Diterpenoids

Sesquiterpenes are not isolated from any extracts, except in a study (Gunbatan et al. 2020), but they were detected in the essential oils of Turkish *Sideritis* species. As diterpenoids, they are abundant compounds isolated from most of the studied *Sideritis* species with diverse carbon skeletons, namely *ent*-kaurane besides labdane, atisane, pimarane, beyerane, trachilobane and rosane (Piozzi et al. 2006). In fact, among investigated *Sideritis* species growing in Turkey, only a few afforded diterpenoids having other skeletons rather than *ent*-kaurene diterpenoids (Table 1).

The first study on diterpenoid components of *Sideritis* species in Turkey was carried out by Sezik et al. (1985). In this study, a labdane diterpene *ent*-2-α-hydroxy-13-*epi*manoyloxide was isolated from *S. perfoliata*.

Baser, Bondi, et al. (1996) studied two species *S. huber-morathii* and *S. caesarea.* From both plants, seven *ent*-kaurene diterpenoids were isolated. Linearol, sidol, candicandiol, siderol, sideridiol and a new compound 3,7,18-triacetylfoliol were isolated from the acetone extract of *S. huber-morathii*, while siderol and epoxysiderol were isolated from *S. caesarea*. The acetone extracts of *S. akmanii*, *S. niveotomentosa*, *S. brevidens*, *S. rubriflora* and *S. gulendamii* were analysed and obtained diterpenoid compounds with *ent*-kaurene skeleton including linearol, isolinearol, foliol, isofoliol, sideridiol, sideroxol, *epi*candicandiol and sidol (Bondi et al. 2000). In a study, the acetone extracts of the three *Sideritis* species were investigated, and *S. libanotica* subsp.

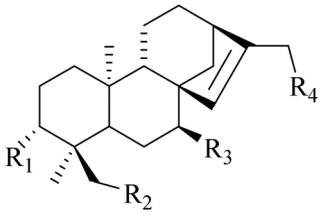
libanotica afforded two *ent*-kaurene diterpenes, siderol and sideridiol, and *S. erythtrantha* var. *erythrantha* gave only sideridiol while *S. perfoliata* afforded three *ent*-kaurene diterpenes. Their structures were elucidated as siderol, sideridiol and sideritriol (Bruno et al. 2005). Four diterpenoids from *S. stricta*; sideridiol, isosidol, isolinearol and linearol were isolated by Şahin et al. (2006). It is obvious that *Sideritis* species do not have very diverse structures in *ent*-kaurene diterpenes. Most of them contain four methyl groups, a hydroxyl group at C-7 and/or C-3, in some cases, one or two methyl groups were oxygenated and converted into acid, aldehyde or hydroxymethylene groups, or converted into exocyclic methylene group. Another species *S. sipylea*, collected from Spil mountain in Manisa-Turkey, afforded three *ent*-kaurene diterpenoids linearol, siderol, *epi*candicandiol. Linearol and *epi*candicandiol were also acetylated and obtained linearol diacetate and *epi*candicandiol diacetate to compare biological activity results by Loğoğlu et al. (2006).

Since over the last 20 years, our group has been continuing systematical investigations on the various species of the genus (*S. arguta*, *S. argyrea*, *S. athoa*, *S. brevidens*, *S. brevibracteata*, *S. condensata*, *S. congesta*, *S. dichotoma*, *S. hololeuca*, *S. leptoclada*, *S. lycia*, *S. niveotomentosa*, *S. sipylea*, *S. stricta*, *S. tmolea* and *S. trojana*) for their diterpenoids with bioactivities. Nine new and 25 known kaurene diterpenoids have been isolated based on spectroscopic methods such as ultraviolet (UV), infrared (IR), one-dimensional and two-dimensional nuclear magnetic resonance (1D- and 2D NMR), mass spectrometry (MS) by Topcu's group and reported in the literature (Topcu et al. 1999, 2001, 2002a, 2002b, 2011; Kilic et al. 2003, 2005, 2009, 2020; Kilic 2006; Carikci et al. 2007, 2012, 2020; Ertaş et al. 2009; Sagir et al. 2017). The new *ent*-kauranes were identified as follows: *ent*-3α,18-dihydroxykaur-16-ene, *ent*-7α,17,18-trihydroxykaur-9(11)-ene-12-one (athonolone), *ent*-7α-15β,16β-poxy-kaurane, *ent*-7α-18-diacetoxy-16β-hydroxykaurane (diacetyldistanol), *ent*-7α-acetoxy-15α,18-dihydroxykaur-16-ene (15-*epi*-eubol), *ent*-7α-acetoxy-16β,18-dihydroxy-kaurane (7-acetyldistanol) and *ent*-1β-hydroxy-7α-acetyl-15β,16β-epoxykaurane. Only two new diterpenoids do not have a kaurane skeleton, which were elucidated as *ent*-6β,8α-dihydroxylabda-13(16),14-diene, and *ent*-2α-hydroxy-8(14),15-pimaradiene; the former one was isolated from *S. argyrea* (Topcu et al. 2001) while the latter one was isolated from endemic *S. trojana* species, which also afforded known compounds siderol, sideridiol, 7-epicandicandiol, isocandol B, candol A acetate and *ent*-7α-acetoxykaur-15-ene (Topcu et al. 2002a).

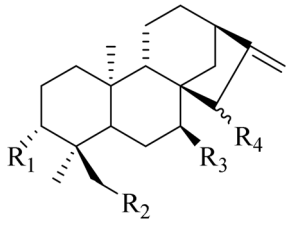
Another endemic species *S. stricta* was studied for phytochemical constituents and structure of isolated diterpenoids was elucidated as sideridiol, isosidol, isolinearol and linearol (Şahin et al. 2006). *S. cypria* Post, collected from Northeastern Cyprus afforded two mixtures of four *ent*-kaurane diterpenes comprising of sidol and isosidol, linearol and isolinearol (Hanoğlu et al. 2019).

Linearol is one of the abundant kaurene diterpenoids, isolated from 16 distinct Anatolian *Sideritis* species, and some derivatives of linearol were prepared by some groups (Topcu et al. 2002b; Loğoğlu et al. 2006; Ozer 2020). Two of the derivatives were identified as *ent*-3α-7β,17-trihydroxy-18-acetoxykaur-15-ene and *ent*-3α-acetoxy-7β,17,18-trihydroxykaur-15-ene, but none of them showed any satisfactory activity against the standard bacteria and some tumour cell lines (Topcu et al. 2002b). The other abundant diterpenoid was identified as siderol in many studies, and acetyl derivative of siderol (siderol acetate) was prepared by Ozer et al. (2019). Sideroxol, which is also a kaurene diterpene, was obtained from the acetone extract of *S. stricta* and its molecular structure and spectral properties were investigated by Azizoglu et al. (2021) (Table 2).

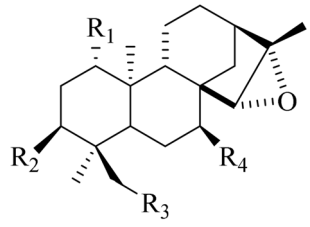
Table 2. Structures of diterpenoids.



	R1	R2	R3	R4
1	H	OH	OAc	H
2	H	OH	OH	H
3	H	OH	OH	OH
4	OH	OH	OH	H
5	OH	OH	OH	H
6	OAc	OH	OH	H
7	H	H	OAc	H
8	H	OH	H	H



	R1	R2	R3	R4
9	OH	OAc	OH	H
10	H	OH	OH	H
11	H	OAc	OH	H
12	H	OH	OAc	H
13	OH	OH	OH	H
14	H	OH	OAc	*β-OH*
15	H	OH	OAc	α-OH
16	H	OH	OH	*β-OH*
17	OAc	OH	OH	H
18	OH	H	H	H
19	OH	H	OH	H
20	OH	OH	H	H
21	H	OH	H	H
22	OAc	OAc	OAc	H

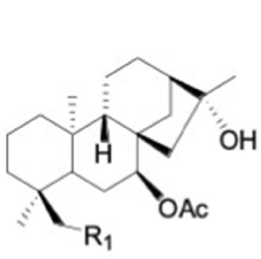


	R1	R2	R3	R4
23	H	OH	OAc	OH
24	H	H	OH	OH
25	H	H	OH	OAc
26	H	H	OAc	OH
27	OH	H	H	OAc

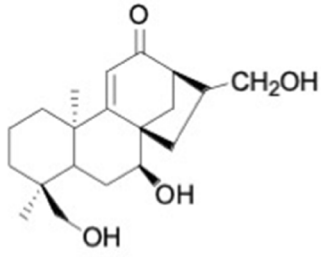
(*Continued*)

Table 2. Continued.

Number	Compound	Number	Compound
1	Siderol (*ent*-7α-acetyl-18-hydroxy-kaur-15-ene)	**16**	Eubotriol (*ent*-7α,15*β*,18-trihydroxy-kaur-16-ene)
2	Sideridiol (*ent*-7α, 18*β*-dihydroxy-kaur-15-ene)	**17**	Sidol (*ent*-3*β*-acetoxy-7α,18-dihydroxykaur-16-ene)
3	Sideritriol (*ent*-7α, 17, 18*β*-trihydroxy-kaur-15-ene)	**18**	*ent*-3*β*-Hydroxy-kaur-16-ene
4	Isolinearol (*ent*-3*β*,7α-dihydroxy-18-acetoxykaur-15-ene)	**19**	*ent*-3*β*,7*α*-Dihydroxy-kaur-16-ene
5	Isofoliol (*ent*-3*β*,7α, 18-trihydroxykaur-15-ene)	**20**	*ent*-3*α*,18-Dihydroxykaur-16-ene
6	Isosidol (*ent*-3*β*-acetoxy-7α,18-dihydroxykaur-15-ene)	**21**	Candol B (*ent*-18-hydroxykaur-16-ene)
7	Isocandol A acetate (*ent*-7α-acetoxy-kaur-15-ene)	**22**	3,7,18-Triacetyl-foliol
8	Isocandol B (*ent*-18-hydroxykaur-15-ene)	**23**	Epoxy-isolinearol (*ent*-3*β*,7α-dihydroxy,18-acetoxy-15*β*,16*β* –epoxykaurane)
9	Linearol (*ent*-3*β*,7α-dihydroxy-18-acetoxykaur-16-ene)	**24**	Sideroxol (*ent*-7α-18-dihydroxy-15*β*,16*β* –epoxykaurane)
10	7-*epi*-Candicandiol (*ent*-7α-,18-dihidroksikaur-16-ene)	**25**	7-Acetoxy sideroxol (*ent*-7α-acetoxy-18-hydroxy-15*β*,16*β*-epoxykaurane)
11	7-*epi*-Candicandiol-18-monoacetate (*ent*-7α-hydroxy-18-acetoxy-16-ene)	**26**	18-Acetyl-sideroxol (e*nt*-7α-hydroxy-18-acetoxy –15*β*,16*β*-epoxykaurane)
12	*ent*-7α-Acetoxy-18-hydroxykaur-16-ene	**27**	*ent*-1*β*-Hydroxy-7α-acetyl-15*β*,16*β*-epoxykaurane
13	Foliol (*ent*-3*β*,7*α*, 18-trihydroxykaur-16-ene)		
14	Eubol (*ent*-7*α*-acetoxy-15*β*,18-dihydroxykaur-16-ene)		
15	15-*epi*-Eubol (*ent*-7α-acetoxy-15α,18-dihydroxykaur-16-ene)		



R_1
28 OAc
29 OH



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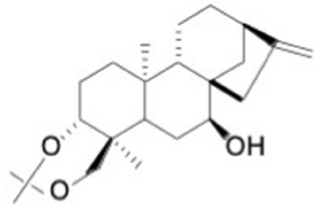

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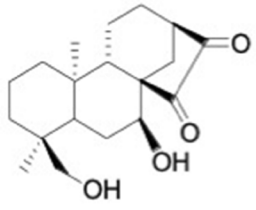

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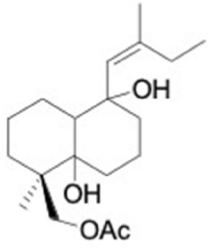

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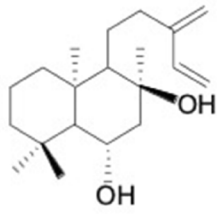

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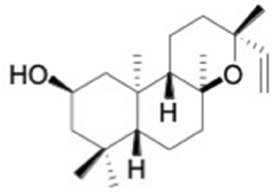

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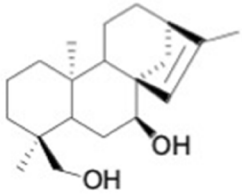

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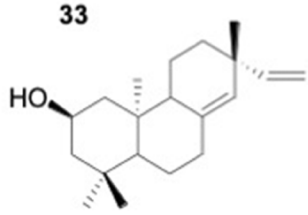


37

28	Diacetyl distanol (*Ent*-7α-,18-diacetoxy-16*β*-hydroxy-kaurane)
29	7-Acetyl distanol (*Ent*-7α-acetoxy-16*β*,18-dihydroxy-kaurane)
30	Athonolone (*ent*-7α,17,18-trihydroxy-9,(11)-ene-12-one)
31	Foliol-3,18-acetonide
32	*ent*-7α,18-Dihydroxy-15-oxokaur-16-ene
33	*ent*-15,16,17,20-Tetra-nor-5,9-dihydroxy-6,19-lacton labda-11-en (lactone diterpene)
34	*ent*-6*β*, 8*α*-Dhydroxy labda-13(16), 14-diene
35	*ent*-2α-Hydroxy-8,13-*β*-epoxy-labd-14-ene
36	*ent*-7α-18-Dihydroxy beyer-15-ene (beyerene diterpene)
37	*ent*-2α-Hydroxy-8(14),15-pimaradiene

Triterpenoids and steroids

Sideritis species are not rich and diverse in triterpenoids and steroids. Squalene as a unique linear triterpene to form other triterpenoids and steroids was found in *S. taurica* Stephan ex Willd, a cultivated species in Egypt (Aboutabl et al. 2002). In fact, this species grows in Bulgaria, Turkey, Crimea and Asia (Fraga 2012). The common triterpenoids ursolic and oleanolic acids have also been isolated from different family plants. In Turkey, particularly Lamiaceae and Boraginaceae family plants are rich in these two triterpenoids. They were found fairly common in *Salvia* species while fairly poor amount in Turkish *Sideritis* species (Özcan et al. 2001) and other Mediterranean *Sideritis* species, such as *S. euboea* Heldr. (Tomou et al. 2020). Besides squalene, α-amyrin and three steroids β-sitosterol, stigmasterol and campesterol were found in the aerial parts of *S. taurica* extract (Aboutabl et al. 2002) while β-sitosterol and its glucoside, and stigmasterol and campesterol identified by high-performance liquid chromatography (HPLC) in *S. montana* seeds extract grown in Turkey (Emre et al. 2011).

On the other hand, palmitic acid, oleic acid and α-linolenic acid were found to be dominant fatty acids of *S. montana* subsp. *montana*. It also bears some steroids consisting of ergosterol, stigmasterol and β-sitosterol, but lipid-soluble vitamins were observed in small quantity (Emre et al. 2011).

Fatty acid compositions of *S. albiflora* and *S. leptoclada* were investigated, and palmitic acid was found as a major fatty acid (Deveci, Tel-Çayan, Duru, et al. 2019; Deveci, Tel-Çayan, Usluer, et al. 2019).

Besides the diterpenoids, the genus *Sideritis* is a rich source of iridoid glycosides, phenylethanoid glycosides, phenolics and flavonoids, particularly flavone glycosides, which are listed in Table 1.

Phenylethanoid glycosides

Acetone extract of *Sideritis ozturkii* afforded three known phenylethanoid glycosides; verbascoside, leucoseptoside A and martynoside (Küpeli, Sahin, Caliş, et al. 2007).

Verbascoside and two flavonoid glycosides, and xanthomicrol were also isolated from *S. stricta* (Küpeli, Sahin, Yeşilada, et al. 2007). In another study on *S. stricta*, phenylethanoid glycoside verbascoside (acteoside) was isolated from acetone extract (Kirmizibekmez et al. 2021).

In fact, verbascoside isolated several *Sideritis* species, which exhibited various activities (Akcos et al. 1999; Adem et al. 2019; Bardakci et al. 2020).

S. cypria was extracted with *n*-butanol and isolated four phenylethanoid glycosides; verbascoside, lavandulifolioside, leonoside A and leucoseptoside A (Hanoğlu et al. 2019).

Phenolics, flavonoids and their glycosides

From aerial parts of *S. perfoliata*, Ezer et al. (1992) isolated three flavonoid glycosides and a phenylethanoid glycoside and their structures were elucidated by spectroscopic methods. Another group investigated the ethyl acetate extract of *S. perfoliata*, which gave 2-oxo-13-*epi*-manoyl oxide (Çelik et al. 2018). In another study on *S. perfoliata* carried out on the extract rich in polar compounds using LC-ESI-MS/MS (liquid chromatography-electrospray ionization-tandem mass spectrometry) (Sarikurkcu et al. 2019), the main compounds were found to be verbascoside, chlorogenic acid and apigenin 7-glucoside. Also in this study, some biological activity results were reported, which mention that the chemical profile is strictly dependent on the extraction solvents as well as the content of the extracts (Table 1).

The methanol extract of an endemic species *S. lycia* afforded four phenylpropanoid glycosides (Akcos et al. 1999). From an endemic species *S. ozturkii*, three new phenylpropanoid flavonoids were isolated and named as ozturkosides A, B and C. The known phenylpropanoid glycosides besides diterpenoids were also isolated by Sahin et al. (2004). Recently, the analysis of phenolic substances was carried out in another collection of *S. ozturkii*'s leaf and flower extracts detected by HPLC (Demirelma and Gelinci 2019), and rutin trihydrate, catechin and trans-*p*-coumaric acid were observed with the highest amount in the leaf extract, while rutin trihydrate, myricetin and trans-p-coumaric acid were found in the flower extract with highest quantities.

From the acetone extract of *S. stricta*, two different isoscutellarein-7-*O*-glycosides, xanthomicrol, were reported by Şahin et al. (2006).

From the methanol extract of *S. brevibracteata*, seven phenolic compounds were obtained while from butanol extract, 7-*O*-glycosides of 8-hydroxyflavones (Güvenç et al. 2010). In another study on *S. brevibracteata*, two glycosides of hypolaetin and two glycosides of isoscutellarein were isolated (Tandogan et al. 2011). Among the five subspecies of *S. libanotica* growing in Turkey, only one of them, *S. libanotica* subsp. *linearis* was studied for phenolic compounds, but only a flavone glycoside was isolated, which showed high antioxidant activity. Also, a kaurene diterpene sideridiol was obtained (Demirtas et al. 2011). Chemical profile of the methanol extract of *S. trojana* was studied by Kirmizibekmez et al. (2012), which detected three flavone glycosides and five phenylethanoid glycosides.

In a recent study, from the acetone extract of *S. caesarea*, two flavonoids and six glycosylated flavonoids were isolated by Halfon et al. (2013). *S. caesarea* was also investigated by another group through bioactivity-guided fractionation and isolation of flavonoids and derivatives. The ethyl acetate fraction afforded four flavonoid glycosides; two of them were obtained as a mixture of 4′-*O*-methylhypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside and isoscutellarein-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside, which showed strong anti-ulcerogenic activity. Structure of the other two flavonoid glycosides was elucidated as 4′-*O*-methylhypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside and isoscutellarein-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside. In addition, a known sesquiterpene glycoside (2*E*,6*E*)-2,6,10-trimethyl-2,6,11-dodecatriene-1,10-diol-1-*O*-β-D-glucopyranoside was obtained (Gunbatan et al. 2020). It is a unique sesquiterpene glycoside, obtained from Anatolian *Sideritis* species.

The wild and cultivated forms of *S. lycia* and *S. libanotica* subsp. *linearis* were investigated by HPLC for phenolic compounds. Major phenolic acids were p-coumaric, caffeic and ferulic acids, while the main flavonoids were quercetin, morin and apigenin. In addition, total phenolics and flavonoids content of both plants were analysed and found that wild plants have higher content than cultivated samples (Dincer et al. 2017).

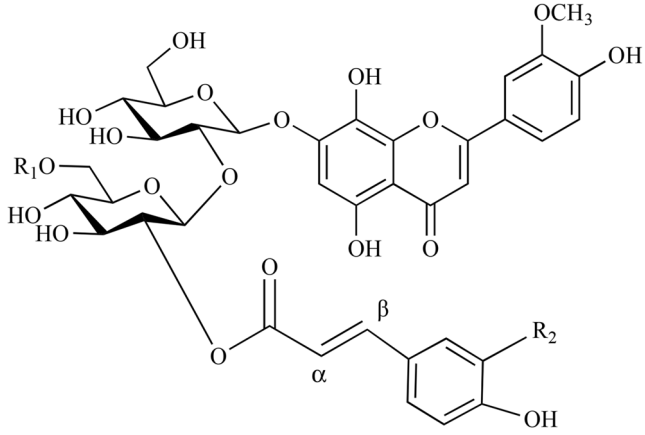
Another species, *S. stricta* was investigated by HPLC with photodiode array detection (HPLC-DAD), and coumarins, catechin hydrate and caffeic acid were found as the major phenolic compounds (Deveci et al. 2018). The LC–MS/MS screening of *S. leptoclada* extracts showed the presence of organic acids, flavonoids and phenolic compounds. Among them, quinic acid, malic acid, chlorogenic acid, syringic acid, p-coumaric acid and vanillic acid were detected in high amounts (Aydoğmuş-Öztürk et al. 2018).

A different study, targeting to find optimal conditions at the highest yield of total polyphenols and flavonoids of *S. montana* with antioxidant activity was carried out by Bilgin et al. (2018) using mathematical models. In the HPLC analysis, rosmarinic acid was identified as the most abundant component, followed by luteolin-3-*O*-glucoside and caffeic acid. For high yield of total polyphenols and flavonoids with the best antioxidant activity, the optimal conditions suggested are 15.02 mL of 22.69% EtOH solution (v/v), 70.16 s, and 9524.52 rpm of mixing speed (Bilgin et al. 2018). In another study, morin, catechin and naringenin were found to be the major flavonoids of *S. montana* (Emre et al. 2011).

The chromatographic separations on the aqueous fraction from *S. congesta* afforded two flavonoid glycosides stachyspinoside, isoscutellarein-7-*O*-(6‴-O-acetyl)-β-allopyranosyl,1→2-β-glucopyranoside and monoterpenoid glucosides betulalbuside A and 1-hydroxylinaloyl-6-*O*-β-D-glucopyranoside (Bardakci et al. 2020).

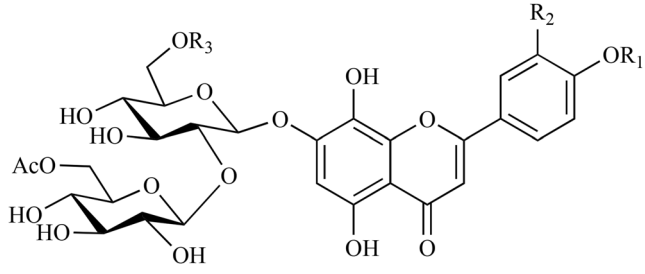
From the aerial parts of *S. cypria* Post, four flavone glycosides, apigenin-7-O-glucopyranoside, isoscutellarein-7-*O*-[6‴-*O*-acetyl-allopyranosyl-(1→2)-glucopyranoside] and a mixture of apigenin-7-*O*-(4″-*O*-*p*-coumaroyl)-glucopyranoside and apigenin-7-*O*-(3″-*O*-*p*-coumaroyl)-glucopyranoside were elucidated (Hanoğlu et al. 2019) (Table 3).

Table 3. Structures of flavonoids.



	R_1	R_2
38	Ac	OH
39	OH	OH
40	Ac	H

Number	Compound
38	Ozturkoside A (chrysoeriol 7-*O*-[2‴-*O*-caffeoyl-6‴-*O*-acetyl-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside])
39	Ozturkoside B (chrysoeriol 7-*O*-[2‴-*O*-caffeoyl-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside])
40	Ozturkoside C (chrysoeriol 7-O-[2‴-*O*-p-coumaroyl-6‴-*O*-acetyl-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside])



	R_1	R_2	R_3
41	H	H	H
42	H	H	Ac
43	H	OMe	Ac
44	Me	H	Ac
45	H	H	Ac
46	H	H	H
47	Me	OH	H
48	H	OH	Ac
49	H	OH	H
50	Me	OH	H
51	Me	OH	Ac
52	H	OMe	Ac

(*Continued*)

Table 3. Continued.

Number	Compound
41	Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside
42	Isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside
43	3′-*O*-Methylhypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside
44	4′-*O*-Methylisoscutellarein-7-O-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside
45	Isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-6‴-*O*-acetyl-*β*-D-glucopyranoside
46	Isoscutellarein 7-*O*-[6‴-*O*-acetyl-*β*-D-allopyranosyl-(1→2)]-*β*-D-glucopyranoside
47	4′-*O*-Methylhypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside
48	Hypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside
49	Hypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside
50	3′-Hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside
51	3′-Hydroxy-4′-*O*-methylisoscutellarein 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside
52	3′-*O*-Methylhypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1 → 2)]-6″-*O*-acetyl-β-D-glucopyranoside

Bioactivity studies on *Sideritis* species

Activity of Sideritis extracts

The interest in *Sideritis* plants and their constituents has increased in recent years, and a number of studies have been published investigating their different activities.

The *Sideritis* plants are commonly consumed as tea, even though some of the species are served as sage tea in the rural area of Anatolia, particularly in the Western Anatolia. Their folkloric uses in the treatment of some diseases are fairly common and back to Dioscorides, especially due to their wound healing and anti-ulcerogenic properties (Yeşlada and Ezer 1989; Gürbüz et al. 2005). In literature, there are several anti-ulcer/anti-inflammatory studies on Anatolian *Sideritis* species (Yeşlada and Ezer 1989; Küpeli et al. 2007; Güvenç et al. 2010) as well as other Mediterranean *Sideritis* species, such as growing in Spain (Barberán et al. 1987).

Investigation of activities of *Sideritis* extracts has recently focused on antioxidant, anti-ulcerative/anti-inflammatory and antimicrobial as well as neuroprotective and memory enhancer activities.

Antioxidant activity

Most of the antioxidant activity studies on Anatolian *Sideritis* plants have been carried out for the extracts using at least two to three complementary methods besides their total flavonoid and phenolic content analyses.

A comprehensive study on antioxidant activity of *Sideritis* species was conducted by Tunalıer et al. (2004) investigating antioxidant activities of phenolic profile of 27 *Sideritis* species. The phenolic components were determined by HPLC-DAD using gallic acid as a standard. The antioxidant activities were measured based on Fe^{2+} induced linoleic acid peroxidation and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity test methods. The amount of phenolic content was higher than 300 $mg_{GAE}/g_{extract}$ for seven species including *S. scardica* subsp. *scardica*, *S. amasiaca*, *S. germanicopolitana* subsp. *viridis*, *S. cilicica*, *S. phlomoides*, *S. gulendamiae* and *S. huber-morathii* while the other 20 species were found to have lower phenolics amount. According to the DPPH radical scavenging activity and lipid peroxidation inhibition activity results, the extracts of *S. scardica* subsp. *scardica*, *S. amasiaca*, *S. germanicopolitana* subsp. *viridis*, *S. germanicopolitana* subsp. *germanicopolitana*, *S. cilicica*, *S. serratifolia*, *S. taurica*, *S. huber-morathii* and *S. armeniaca* showed remarkable activity in both test methods. Also, the study was clearly pronounced that the species, which have the highest amounts of phenolics, showed the highest antioxidant activity (Tunalier et al. 2004).

Methanol extracts of *S. condensata* and *S. erythrantha* var. *erythrantha* extracts were also investigated for total phenolics, anti-radical activities and antioxidant activities. The amount of phenolic contents of *S. condensata* extract was found to be higher than that of *S. erytrantha* var. *erythrantha* (247.62 ± 1.91/217.61 ± 0.95 mg GAE/g). The free radical scavenging activity by DPPH test assay and the antioxidant capacity by phosphomolybdenum test assay were measured, and the free radical scavenging activity of the extracts showed moderate activity (Ozkan et al. 2005).

Güvenç et al. (2005) have studied antioxidant activity of lyophilized extract of 17 *Sideritis* species including *S. albiflora*, *S. arguta*, *S. brevibracteate*, *S. condensata*, *S. congesta*, *S. dichotoma*, *S. erythrantha* var. *cedretorum*, *S. erythrantha* var. *erythtrantha*, *S. huber-morathii*, *S. leptoclada*, *S. libanotica* subsp. *libanotica*, *S. phrygia*, *S. pisidica*, *S. rubiflora*, *S. serratifolia*, *S. sipylea*, *S. syriaca* subsp. *nusarensis* and *S. tmolea*. For determination of the antioxidant activity, the DPPH assay with a rapid TLC (thin-layer chromatography) screening method was used, and *in vitro* antioxidant activity was carried out by lipid peroxidation of liposomes where thiobarbituric acid (TBA) was used. The DPPH results of the most extracts showed strong activity except *S. erythrantha* var. *erythtrantha*, *S. dichomata*, *S. syriaca* subsp. *nusairiensis* and *S. tmolea*. In the lipid peroxidation assay, high activity was observed only for the *S. brevibracteate* and *S. condensata* extracts.

Nakiboglu et al. (2007) examined water, ethanol, methanol and acetone extracts of *S. sipylea* for their DPPH free radical scavenging activity and hydroxyl anion radical scavenging activity. The phenolic content of *S. sipylea* was found to be in decreasing ratio from methanol extract to ethanol, acetone and water extracts. Methanol and acetone extracts of *S. sipylea* showed good hydroxyl radical scavenging activity while methanol and ethanol extracts of *S. sipylea* showed good radical scavenging activity. Total antioxidant capacity was also determined by the thiocyanate method, which showed similar results. As a result, *S. sipylea* was found to be a promising antioxidant source despite not to study yet for polar compounds.

Methanol extracts of *S. huber-morathii* and two endemic species *S. ozturkii* and *S. caesarea* were investigated for total phenolic and flavonoid contents besides antioxidant and antimicrobial activities (Sagdic et al. 2008). *S. caesarea* had a higher percentage of the total phenolic, flavanol and flavonol contents than those of *S. ozturkii*. Antioxidant activity was tested only by DPPH radical scavenging activity. Antimicrobial activity of the extracts was tested at different concentrations on 15 microorganisms. Both activity results showed that the extracts of two plants have high antioxidant and antimicrobial activity. In another study conducted by Zengin et al. (2019), the methanol extract of *S. ozturkii* showed a very high antioxidant activity.

Infusion of *S. leptoclada* was studied by Ayar-Kayalı et al. (2009) for total phenolic compounds, the hydroxyl anion (OH) radicals and DPPH radical scavenging activities, which exhibited high scavenging activities against both radicals.

The methanol and acetone extracts of *S. arguta* (Ezer et al. 1992) exhibited fairly good lipid peroxidation inhibitory activity in β-carotene linoleic acid assay with half maximal inhibitory concentration (IC_{50}) values of 2.60 ± 0.6 and 4.79 ± 0.7 µg/mL, respectively, while in the DPPH assay, they showed moderate activity with IC_{50} values of 35.54 ± 0.4 and 23.61 ± 0.4, respectively. However, a very weak superoxide anion radical scavenging activity was observed in petroleum ether, acetone and methanol extracts.

Erdogan-Orhan et al. (2010) screened antioxidant activities of sage-called plants including *Salvia* and *Sideritis* species. For this purpose, 87 plant samples were bought from different herbalists. Infusion samples of the species were tested for antioxidant activity and acetyl cholinesterase (AChE) inhibitory activity. DPPH radical scavenging, ferrous ion-chelating and ferric reducing antioxidant power (FRAP) test results exhibited that *S. arguta* and *S. congesta* infusions had highest scavenging effects, and particularly *S. arguta* gave high FRAP activity. However, all samples displayed an insignificant effect on the ferrous-ion chelating. It was interesting that anti-AChE activity was not observed for any of *Sideritis* species tested.

In the study conducted by Emre et al. (2011), *S. montana* subsp. *montana* was analysed for non-polar compounds including fatty acids, steroids, levels of lipid-soluble vitamins, as well as flavonoids and antioxidant properties. The methanol extracts of *S. montana* were investigated for antioxidant properties while the fatty acids, vitamins and flavonoid extracts were tested on microorganisms such as *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*.

Dorman et al. (2011) reported that three *Sideritis* species; *S. dichotoma*, *S. erythrantha* var. *cedrotorum* and *S. vuralii* were extracted and investigated for their total phenolics, iron(III) reductive effects and DPPH radical scavenging activities. *Camellia sinensis* (L.) Kuntze (Theaceae) was also prepared for use as a positive control for comparison in all tests. But none of the extracts was found to be as active as with positive controls ascorbic acid, BHA and Trolox.

Erkan et al. (2011) have evaluated antioxidant activities of two endemic species; *S. congesta* and *S. arguta*. The extracts of *S. arguta* were found to be more active than *S. congesta*. Also, both species were analysed for free flavonoids and cinnamic acids using HPLC-DAD. Methanol, ethylacetate and acetone extracts of the two species were found to be rich in cinnamic acid derivatives, the most abundant ones being ferulic and chlorogenic acids. As the flavonoids, *S. arguta* contained higher number of flavonoids such as quercetin, kaempferol and apigenin. However, quercetin was not found in *S. congesta*. Both acetone and methanol extracts of *S. arguta* were found to be more potent than other extracts tested for DPPH free and $(ABTS)^+$ cation radical scavenging activities.

In another study, five extracts of *S. congesta* plant were prepared in different solvents, and they were evaluated by complementary anti-oxidant activity tests (DPPH radical scavenging, FRAP, CUPRAC and total antioxidant capacity), and the ethyl acetate fraction exhibited the highest phenolic content with the highest antioxidant activity and rich in verbascoside and martynoside content (Bardakci et al. 2020).

Tekeli (2012) has investigated antioxidant activities and phenolic compositions of *S. phrygia* and *S. bilgerana*. Radical scavenging activities were determined based on DPPH and FRAP tests. The results indicated that *S. phrygia* showed higher antioxidant capacity than *S. bilgerana*.

Different parts (flower, leaf, seed) of *S. condensata* were infused at different temperatures and times to investigate their phenolic composition and antioxidant activities. Phenolic compounds were analysed by using HPLC. Antioxidant activity was determined based on DPPH radical scavenging method. Eventually, the leaves of the *S. condensata* were prepared in hot water at 100 °C for 5, 10 and 30 min, which has the highest total phenolics and the strongest antioxidant activity (Kara et al. 2014).

Antioxidant properties of the infusion and decoction of *S. athoa* and *S. perfoliata* were determined based on DPPH, β-carotene linoleic acid and cupric (Cu^{2+}) ion reducing power assay (CUPRAC). Tea samples showed high antioxidant activity in all methods (Carikci 2020).

A study was conducted using different extraction methods to determine the most effective extract in antioxidant capacity and enzyme inhibition activity (Celep et al. 2019). For this purpose, *S. trojana* extracts were prepared by infusion, decoction, ultrasonic assisted and chemical extraction methods. No significant difference was observed between the infusion and decoction methods in terms of the parameters studied. However, the extract with the highest phenolic content showed the highest antioxidant capacity. In addition, the related enzyme inhibition results showed that the plant is a good source of postprandial diabetes (Celep et al. 2019).

Cholinesterase and other enzyme inhibitory activities

The acetone, methanol and water extracts of *S. caesarea* investigated the acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities at 200 µg/mL. The water extract exhibited better activity against the enzyme AChE compared to both the acetone and methanol extracts (Halfon et al. 2013).

Methanol and hexane extracts of *Sideritis libanotica* subsp. *linearis* Labil on AChE enzyme were investigated *in vitro*. Human serum and erythrocytes were used as enzyme sources. While the hexane extracts did not show any inhibitory effect on erythrocyte AChE levels, the methanol extracts had very low inhibition values (Korkmaz et al. 2017).

In another study, the infusion and decoction tea samples prepared from both *S. perfoliata* subsp. *athoa* and *S. trojana* showed inhibitory activities against AChE and BChE enzyme investigated by Carikci (2020). Decoction samples of *S. trojana* had the highest inhibition rate against both enzymes among the studied samples.

A study was carried out by Çelik and Kaya (2011) for antioxidant activity of *S. caesarea* infusion against tricyclic antidepressant (TCA) effects in rats. Glutathione reductase (GR), superoxide dismutase (SOD), glutathione-S-transferase, catalase (CAT), GSH level and malondialdehyde (MDA) content in various organs of rats were selected for monitoring activities. The study showed that *S. caesarea* had protective effects against chemical-induced oxidative injury.

Zengin et al. (2014) evaluated antioxidant and enzyme inhibitory potential of different extracts of *S. galatica*. Petroleum ether, ethyl acetate, methanol and water extracts were prepared to determine total phenolic and flavonoid, total saponins, total condensed tannin and total flavonol contents. Also, the extracts were tested for antioxidant abilities using free radical scavenging (DPPH, ABTS and nitric oxide (NO)), reducing power (FRAP and cupric reducing antioxidant capacity (CUPRAC)), total antioxidant capacity and metal chelating test assays. Their cholinesterase, α-amylase and α-glycosidase inhibition activities were also determined. As a result, *S. galatica* might be useful as a natural source for antioxidant, anti-Alzheimer and type II diabetes.

Both *S. albiflora* and *S. leptoclada* species were found to be rich in rosmarinic acid and caffeic acid. The acetone extracts

exhibited the highest activity in terms of antioxidant activity, while the hexane extracts showed superior urease inhibitory activity (Deveci, Tel-Çayan, Duru, et al. 2019; Deveci, Tel-Çayan, Usluer, et al. 2019).

The hexane and methanol extracts of *S. albiflora*, *S. stricta*, *S. pisidica* and *S. leptoclada* were investigated in terms of antidiabetic activity on α-glucosidase and α-amylase enzymes (Deveci et al. 2020). The hexane extract *S. pisidica* exhibited higher α-amylase inhibitory activity than the other plant extract, even standard compound while *S. leptoclada* hexane extract was found to be more effective than of *S. stricta* for α-glucosidase inhibitory activity. Therefore, the authors suggested that hexane extract of *S. pisidica* might be a potential antidiabetic agent.

Kirmizibekmez et al. (2021) investigated *S. germanicopolitana* phytochemically for anticholinesterase and LOX inhibitory effects, and all the isolated compounds (**1–14**) showed low to moderate tested activities.

The enzyme inhibitory activities (against AChE and BChE, tyrosinase, α-glucosidase and α-amylase) of *S. perfoliata* were investigated besides antioxidant activities (Sarikurkcu et al. 2019).

Sarikurkcu et al. (2021) further investigated another species *S. leptoclada* EtOAc extract for antioxidant and inhibitory effects of two enzymes, and the extract showed fairly high α-amylase inhibitory activity (2.21 mg/mL). Docking analysis showed that verbascoside, one of the important constituents of *Sideritis* species, was found to be an effective agent as tyrosinase and α-amylase inhibitory activity (Sarikurkcu et al. 2021).

Antimicrobial activity

Antimicrobial activity studies for over 30 Anatolian *Sideritis* species have been reported so far in the literature.

Antimicrobial activities of *S. condensata* and *S. erythrantha* var. *erythrantha* extracts were investigated besides the antioxidant activities (Ozkan et al. 2005). For antimicrobial activity test, the agar diffusion method was used, the most sensitive bacterium was *Pseudomonas aeruginosa* while the most resistant bacterium was *Enterococcus faecalis* for the *S. condensata* extract. For the *S. erythrantha* var. *erythrantha* extract, *E. faecalis* was found as the most sensitive and *S. aureus* as the most resistant.

The methanol extracts of *S. brevidens*, *S. cilicica* and *S. vuralii* were investigated for their antimicrobial activity. A series of microorganisms are used to determine activity by disk diffusion method as follows: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Bacillus cereus*, *Mycobacterium smegmatis*, *Listeria monocytogenes*, *Micrococcus luteus*, *Candida albicans*, *Rhodotorula rubra* and *Kluyveromyces fragilis*. The three *Sideritis* extracts investigated were found to be effective against all the tested microorganisms. But all the species were not effective against *Micrococcus luteus* and *Proteus vulgaris*. The bacteria *Listeria monocytogenes*, *Bacillus cereus* and *Klebsiella pneumoniae* were especially sensitive to the extract of *S. cilicica*. Moreover, the antifungal effect of *Sideritis* species was found to be much less compared with the standard antifungal antibiotics (Dulger, Gonuz, et al. 2005; Dulger, Ugurlu, et al. 2005).

The other antimicrobial activity on *Sideritis* species also conducted by Dulger, Gonuz, et al. (2005) and Dulger, Ugurlu, et al. (2005) was on the three endemic species *S. albiflora*, *S. brevibracteata* and *S. pisidica* on microorganisms *E. coli*, *S. aureus*, *K. pneumoniae*, *M. luteus*, *Micrococcus flavus*, *P. vulgaris*, *P. aeruginosa*, *Corynebacterium xerosis*, *M. smegmatis*, *B. cereus*, *Bacillus subtilis*, *C. albicans*, *Saccharomyces cerevisiae*, *K. fragilis* and *R. rubra*. No significant activity was found against *S. aureus*, *M. flavus*, *M. luteus*, *P. vulgaris* or the acid-fast bacterium *M. smegmatis*. The extracts of three endemic *Sideritis* species exhibited the highest activity against *B. subtilis*, *E. coli*, and especially *P. aeruginosa* and against all yeasts tested. Only the chloroform fraction of *S. brevibracteata* exhibited antimicrobial activity, but the extracts of methanol, H_2O and n-BuOH did not.

Fifteen plants used in Turkish folk medicine were investigated for their antimicrobial activity by Tosun et al. (2006). Six bacteria species were used as test microorganisms and *S. galatica* (used for appetizing and carminative) exhibited high activity against only two microorganisms: *C. albicans* and *C. krusei*.

The anticandidal activity of the methanol extracts of *S. dichotoma*, *S. trojana*, *S. sipylea*, *S. rubriflora*, *S. bilgerana*, *S. galatica* and *S. condensata* was evaluated against clotrimazole-resistant *Candida albicans* (Dulger et al. 2006). Among the seven *Sideritis* species, *S. trojana* and *S. bilgerana* were found to be the most active.

Methanol extract of two endemic *Sideritis* species: *S. caesarea* and *S. vuralii* were tested against four fungi. Both species showed no fungicidal activity, but fungistatic activity (Askun et al. 2008).

The antifungal activity of *S. germanicopolitana* methanol extract and essential oil was carried out against four fungi species, and results showed that antifungal capacity of the plant might be used for controlling plant diseases (Bayan and Aksit 2016).

The antimicrobial effect of the leaf extract of *S. ozturkii* against standard bacteria such as *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus* and *E. faecalis* was investigated by liquid microdilution method, and MIC values were determined (Gelinci et al. 2020).

The antifungal capacity of the chloroform extracts of *S. montana* (Balkan et al. 2019) was found extremely low. However, the radical scavenging capacity of *S. montana* was found to be significantly high.

Cytotoxicity/anticancer activity

Demirtas et al. (2009) investigated antiproliferative effects on African green monkey kidney (Vero), human uterus carcinoma (HeLa) and rat brain tumour cells (C6) of the methanol extract of *S. libonatica* subsp. *linearis*. The extract was found to be active against all the tested cells.

The acetone extract of *S. lycia* has evaluated cytotoxic activity against a panel of cell lines (human breast cancer (BC1), human lung cancer (LU1), human colon cancer (COL2), drug resistance (KB and KB-VI), human prostate cancer (LNCaP) and mouse lymphocytic leukaemia (P388) HTERT RPE, and A2780) *in vitro* and exhibited moderate activity against some of the cell lines (Kilic et al. 2020).

The singlet oxygen production capacity, cytotoxicity against malignant melanoma cancer (HT-144) and fibroblast (3T3) cell lines of *S. leptoclada* extracts were investigated. In the standard MTT assay, growth of HT-144 cell lines inhibited by the ethanol extract of *S. leptoclada* triggered apoptotic cell death, possibly by ROS apparently produced by TNF-α secretion. These results showed that *S. leptoclada* may be used in the treatment of treatment-resistant malignant melanoma cancer (Aydoğmuş-Öztürk et al. 2018).

In vitro antibacterial and antitumour activity of aqueous methanol and ethanol extracts of *S. taurica* Steph. ex Willd. was detected with 10 different species from Turkey (Turker et al. 2018). The alcoholic extracts of *S. taurica* showed the high antibacterial activities against tested bacteria and comparatively moderate antitumour efficiency.

The water extract of *S. ozturkii* slightly inhibited growth of human breast cancer cell line (MDA-MB-231 cells) whereas the

ethyl acetate and methanol extracts showed strong inhibition of MDA-MB-231 cells and caused apoptotic cell death (Zengin et al. 2019). Other study conducted on the methanol extract of *S. ozturkii* on DLD-1 human colorectal cancer cells exhibited cytotoxicity in a dose- and time-dependent manner (Demirelma and Gelinci 2019).

S. perfoliata methanolic extract showed cytotoxic activity on the HeLa cells (cervical cancer cells) in dose depending manner besides moderate antioxidant activities (Cocelli et al. 2021).

S. niveotomentosa extracts, especially methanol extract, are rich in phenolic compounds and showed a strong radical scavenging activity. Furthermore, the extracts demonstrated selective cytotoxic activity on the DLD1, HL60 and ARH77 cell lines (Sezer and Uysal 2021).

Central nervous system/insecticidal activities

The effects of ethanolic extracts of *S. arguta*, *S. pisidica*, *S. argyrea*, *S. libanotica* ssp. *linearis*, *S. perfoliata* and *S. congesta* were tested on carrageenan-induced hind paw oedema in mice to determine the anti-inflammatory activities. The extracts, except *S. congesta*, significantly inhibited the oedema. Also, it was found that the anti-inflammatory activity reached a peak 4 or 5 h after carrageenan administration (Yeşlada and Ezer 1989).

The insecticidal activity of the acetone extract of *S. trojana* investigated against *Acanthoscelides obtectus*, *Sitophilus granarius* and *Ephestia kuehniella*, which are very important stored pests in the world. It was showed that the extract killed *A. obtectus* and *S. granarius* effectively (Aslan et al. 2006).

The toxicity of the acetone extract of *S. condensata* investigated insecticidal activity, which has been determined against *Bemicia tabaci*, *Lasioderma serricorne*, *Tetranychus urticae*, *S. granarius*, *A. obtectus* and *E. kuehniella*. The acetone extract of *S. condensata* showed high toxicity against *B. tabaci* and *L. serricorne* with a 78% and 73% of mortality rate, respectively (Kilic et al. 2009).

Antiulcer activity studies

Since some *Sideritis* species are commonly used for treatment of several peptic ulcer symptoms such as stomachache and heartburn, traditionally, anti-ulcerogenic activity of some species was investigated *in vitro* and *in vivo*. One of the investigated species for this purpose was *S. caesarea*. The decoctions of plants were prepared and *in vivo* anti-ulcerogenic activity tested by ethanol-induced ulcerogenesis method, determined healing effects through histopathological evaluation. *S. caesarea* was protected three out of six rats from any visible damage. The extract was treated with lamina epithelialis; these findings may support the intended use of the species (Gürbüz et al. 2005). In another study on the same plant, the ethanol (80%) extract showed potent anti-ulcerogenic activity. Among the liquid–liquid fractions, the ethyl acetate fraction showed strongest anti-ulcerogenic activity; therefore, bioactivity guided fractionation studies were carried out on the ethyl acetate fraction of *S. caesarea*, which afforded two anti-ulcerogenic flavonoid glycosides (Gunbatan et al. 2020).

Other activity studies

An interesting study was conducted by Öztürk et al. (1996) to evaluate the effects of four *Sideritis* extracts on the central nervous system (CNS) by comparison with two antidepressant drugs using a swimming test on mice and rats. Four *Sideritis* species: *S. libanotica* subsp. *kurdica*, *S. lanata*, *S. perfoliata* and *S. athoa* were extracted with water and lyophilized, and then their aqueous extracts injected mice with and without antidepressant desipramine and trimipramine at different doses. The results showed that *Sideritis* extracts had some activity on the CNS on mice. At a low dose, the extracts caused inhibition on swimming performance suggesting a depressive effect on the CNS. At higher doses, except *S. perfoliata* and *S. athoa* extracts, the swimming time of mice was increased. The study pointed out that *Sideritis* species have shown more or less sedative and stimulant effects.

In one of another recent studies, investigations on a methanolic extract of *S. bilgeriana* exhibited could be useful for inflammation and neuropathic pain management, mainly in the management of pro-inflammatory mediators (NF-κB, TNF-α, IL-1 β and IL-6) (Cavalcanti et al. 2021).

Activities of the essential oils, isolated compounds/components

Activity of the essential oils

Essential oils of some *Sideritis* species have been investigated for some activities.

Antioxidant activity

The antioxidant activities of two varieties of *S. erythrantha* essential oils are investigated by Köse et al. (2010). The antioxidant activity of the essential oils has been determined by three different test systems: DPPH, β-carotene/linoleic acid and reducing power. In the three methods, the two oils showed weak antioxidant activity.

Antimicrobial activity

Iscan et al. (2005) analysed *S. cilicica* and *S. bilgerana* essential oils and their antimicrobial activity. The essential oils of both showed significant inhibitory effects against *Candida albicans* and microbial effects on human pathogenic bacteria methicillin-resistant *Staphylococcus aureus* (MRSA).

The essential oils of *S. curvidens* Staph and *S. lanata* were investigated for antimicrobial activity by Uğur et al. (2005). The antibacterial effects were tested on *S. mutans*, *S. aureus*, *S. aureus*, *S. epidermis*, *M. luteus*, *B. subtilis*, *B. cereus*, *E. coli*, *P. aeruginosa*, *S. sonnei*, *E. aerogenes* and *S. typhimurium*. The essential oils of the species had a strong activity against Gram (+) bacteria, especially MRSA and oxacillin resistant coagulase negative *Staphylococcus epidermis*. Also, *Bacillus cereus* and *B. subtilis* had sensitivity to essential oils. In addition, the essential oils of the two species were more effective than the antibiotics, which were used in this study.

The antimicrobial activities of two varieties of *S. erythrantha* essential oils are investigated by Köse et al. (2010). The two oils exhibited moderate activity against Gram (+) and only two of the Gram (–) bacteria were tested. *S. erythrantha* var. *cedretorum* essential oil was as effective as the antibiotic against vancomycin-resistant *enterococci* (VRE), ampicillin-resistant *Haemophilus influenza*, strongly, MRSA and vancomycin sensitive *E. faecalis*. *S. erythrantha* var. *erythrantha* essential oil was also as effective as the antibiotic against VRE and ampicillin resistant *H. influenzae*.

The other activity study on *S. erythrantha* var. *erythrantha* essential oil was carried out by Altundag et al. (2011). The essential oil was evaluated for antimicrobial activity against 19 phytopathogenic bacteria and inhibited only five pathogenic bacteria. The essential oil of *S. erytrantha var. erytrantha* was further investigated against

Xanthomonas vesicatoria, the agent of bacterial spot of tomato, and found no activity (Altundag and Aslim 2011).

Cytotoxicity/anticancer activity

The potential oxidative capacity of *S. stricta* was investigated against parental and epirubicin-HCl resistant H1299 cells. Relying on time and concentration, the essential oil of *S. stricta* showed cytotoxic and more selective effects and caused an increase in MDA level on both parental and drug resistant H1299 cells (Erdoğan et al. 2018).

Central nervous system/insecticidal activities

In a recent study, insecticidal activity of *S. perfoliata* essential oil was tested on two important pest insects, *A. obtectus* and *Tribolium castaneum* by Karaborklu (2014). Essential oil, having α-pinene, β-phellandrene and β-pinene as the main constituents, caused 100% mortality on *A. obtectus* adults, 76.7% mortality on the *T. castaneum* adults.

Other activity studies

Aydın et al. (1996) investigated analgesic activity of essential oil of *S. congesta*, which consists of mainly α- and β-pinenes, but the essential oil of *S. congesta* did not show significant analgesic activity.

Activities of the diterpenoids

Some activity studies on the isolated diterpenoids from Anatolian *Sideritis* species have been carried out over the last 25 years (Topcu and Goren 2007; Kilic et al. 2020).

Antioxidant activity

The antioxidant potential of 11 isolated diterpenoids 7-acetyldistanol, epoxyisolinearol, sideroxol, sideridiol, siderol, 7-*epi*-candicandiol, linearol, sidol, diacetyl distanol, eubol and eubotriol was determined by three methods including β-carotene bleaching method, free radical scavenging activity and superoxide anion scavenging activity. Only 7-acetyldistanol, epoxyisolinearol and 7-*epi*-candicandiol have showed lipid peroxidation inhibitory activity (Topcu et al. 2011).

Cholinesterase and other enzyme inhibitory activities

Acetylcholinesterase and BChE inhibitory activities of diterpenes isolated from *S. arguta* were evaluated, and the *ent*-kauranes eubol, sideroxol and 7-*epi*-candicandiol exhibited moderate-high BChE inhibitory activity, but not active against AChE enzyme (Ertaş et al. 2009).

Inhibition effect of 11 isolated diterpenoids 7-acetyldistanol, epoxyisolinearol, sideroxol, sideridiol, siderol, 7-*epi*candicandiol, linearol, sidol, diacetyl distanol, eubol and eubotriol was carried out against two enzymes, AChE and BChE, by the Ellman method. While the tested *ent*-kaurenes had no inhibitory activity on the AChE enzyme, three of them: eubol, sideroxol and 7-*epi*candicandiol showed moderate activity against BChE (Topcu et al. 2011).

Antimicrobial activity

Kilic et al. (2003) have investigated five kaurene diterpenoids (linearol, foliol, 7-*epi*-candicandiol, siderol and sideroxol) isolated from different *Sideritis* species against *B. subtilis*, *S. aureus*, *P. aeruginosa*, *S. epidermidis*, *Proteus mirabilis*, *E. coli*, *K. pneumonia*, *E. faecalis* and *C. albicans*. 7-*Epi*-candicandiol has the highest activity against *E. coli*, also showed good activity against *S. aureus*, *P. aeruginosa*, *K. pneumonia* and *E. faecalis* while sideroxol was found to be moderately active against *B. subtilis*.

Eight kaurane diterpenoids (*ent*-1β-hydroxy-7α-acetyl-15β, 16β-epoxykaurane, sideroxol, 7-acetyl sideroxol, 7-*epi*-candicandiol, linearol, foliol, sideridiol and siderol) were evaluated antimicrobial and antifungal activity against *E. coli*, *S. aureus*, *K. pneumonia* and *C. albicans* (Kilic 2006). But none of the compounds showed noticeable activity.

Loğoğlu et al. (2006) isolated and investigated biological activity of diterpenoid compounds from *S. sipylea*. The isolates linearol, siderol and 7-*epi*candicandiol were tested against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa* and *C. albicans*. The results indicated that only 7-*epi*-candicandiol showed meaningful activity against some of the tested bacteria, and this effect is reduced by the presence of the acetyl group.

The kaurene diterpenoids 7-*epi*-candicandiol, sidol, siderol, sideridiol and linearol were tested against a panel cell lines for antimicrobial activities. Among the tested *ent*-kaurene diterpenoids, 7-*epi*-candicandiol showed fairly high activity (Topcu and Goren 2007).

Cytotoxicity/anticancer activity

The cytotoxic activity on cancer cell lines of linearol, sidol 7-*epi*-candicandiol, siderol and sideridiol isolated from *S. lycia* was investigated. Only 7-*epi*-candicandiol showed meaningful results against a series of cancer cell lines with ED_{50} values; KB (13.3 μg/mL), COL-2 (11.8 μg/mL), LU1 (17.9 μg/mL), LNCaP (14.9 μg/mL) and A2780 (9.0 μg/mL) (Kilic et al. 2020).

Central nervous system/insecticidal activities

The insecticidal activity of *ent*-kaurene diterpenoids 7-*epi*-candicandiol and 18-acetylsideroxol, isolated the acetone extract of *S. trojana*, and acetylation product of 7-*epi*-candicandiol (7-*epi*-candicandiol diacetate) was investigated by Aslan et al. (2006). The isolates 7-*epi*-candicandiol and 18-acetylsideroxol killed *A. obtectus* and *S. granarius* effectively. However, 7-*epi*-candicandiol diacetate exhibited medium mortality rate against *E. kuehniella*.

Kilic et al. (2020) also investigated insecticidal activity of main components of *S. lycia*, linearol, *Tetranychus urticae*, *Bemicia tabaci*, *S. granaries* and *Lasioderma serricorne*. Linearol had a statistically significant effect on mortality of all tested insects at 95% confidence level (Kilic et al. 2020).

Based on these results, kaurene diterpenoids could be potential source to be used in sustainable pest management.

Other activity studies

Effects of linearol, isolinearol, foliol, isofoliol, sideridiol, sideroxol, *epi*-candicandiol and sidol isolated from four *Sideritis* species on the feeding behaviour of the final stadium larvae of the *Lepidoptera*, *Spodoptera frugiperda* and *S. littoralis* were determined (Bondi et al. 2000). Sideroxol was the only active diterpenoid tested against *S. frugiperda* to cause significant antifeedant activity, while none of the four compounds tested against *S. littoralis* showed significant antifeedant activity. Also, the results showed that foliole was a potent phagostimulant for *S. littoralis*. Comparison of the activity results showed that the presence of an epoxide group in the structure of the sideroxol might contribute to the activity.

The *in vitro* antiviral index (AI) of linearol, sidol and isosidol isolated from *S. lycia* was determined (Kilic et al. 2020). The CD_{50} values of the tested compounds, for the viability of Vero cells, were determined as 29.32, 14.64 and 27.27 μg/mL, respectively. The most active compound was found to be isosidol. AI

values of linearol and isosidol were close to each other while sidol was found to be inactive.

Activities of the flavonoids and other phenolics

Antioxidant activity. The antioxidant activity of seven phenolic compounds, 7-*O*-glycosides of 8-OH-flavons (hypolaetin, isoscutellarein and their methyl ethers and verbascoside) from *S. brevibracteata* was investigated using TBA method. The highest activity was observed for hypolaetin derivatives and verbascoside. Among the flavone glycosides, hypolaetin derivatives were also found to have stronger activity than isoscutellarein (Güvenç et al. 2010).

The methanol extract of *S. libanotica* subsp. *linearis* and isolated flavone 3′-*O*-methylhypolaetin 7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside showed high antioxidant activity in total reduction power and free radical scavenging activity tests (Demirtas et al. 2011).

All isolated flavone glycosides and phenylethanoid glycosides from the methanol extract of *S. trojana* were tested for antioxidant activity by *in vitro* Trolox equivalent antioxidant capacity (TEAC) assay (Kirmizibekmez et al. 2012). Among them, the most active ones were also investigated for their ability to reduce reactive oxygen species (ROS) levels in human prostate cancer cells (PC3) exposed to the oxidant *tert*-butylhydroperoxide. Isoacteoside and isoscutellarein 7-*O*-[6‴-*O*-acetyl-β-allopyranosyl-(1→2)]-β-glucopyranoside showed significant reduction of ROS levels (Kirmizibekmez et al. 2012).

Central nervous system/insecticidal activities. From the methanol extract of *S. lycia*, four phenylethanoid glycosides: lavandulifolioside, martynoside, verbascoside (acteoside) and leucosceptoside A were screened for anti-inflammatory activity using the carrageenan-induced mouse paw edema (CPE) (Akcos et al. 1999). It is noted that flavonoid glycosides showed higher activity than phenylethanoid glycosides. Also, gastric ulceration studies of these compounds were investigated, and found that the gastric ulceration effects of phenylethanoid glycosides were weaker than those of flavonoid glycosides.

Küpeli, Sahin, Yeşilada, et al. (2007) studied *in vivo* anti-inflammatory and antinociceptive activities of the isolated compounds from two *Sideritis* species; *S. ozturkii* (Küpeli, Sahin, Caliş, et al. 2007) and *S. stricta*. The compound ozturkoside C was found to be the most active one and the phenolic fraction of *S. ozturkii* displayed strong inhibitory activity on mice. In contrast, phenolic fraction of *S. stricta* did not display significant activity. However, verbascoside and a mixture of two flavonoid glycosides exhibited remarkable inhibitory effect at high dose.

The isolated seven phenolic compounds, 7-*O*-glycosides of 8-OH-flavones (hypolaetin, isoscutellarein and their methyl ethers) and verbascoside from *S. brevibracteata* and fractions were investigated to determine their anti-inflammatory, antinociceptive activities. The *in vivo* anti-inflammatory activity was determined using carrageenan-induced hind paw edema model, prostaglandin (PGE_2)-induced hind paw edema model and TPA-induced mouse ear edema model. The antinociceptive activity was realized through p-benzoquinone (PBQ)-induced abdominal constriction test on mice. The highest anti-inflammatory and antinociceptive activity was shown by *n*-butanol fraction and its isolates. Verbascoside was found to be active in all the tested systems as well as hypolaetin derivatives (Güvenç et al. 2010).

Cholinesterase and other enzyme inhibitory activities. The isolated compounds 7-*O*-glycosides of 8-OH-flavones (hypolaetin, isoscutellarein and 3′-hydroxy-4′-*O*-methylisoscutellarein) from *S. brevibracteata* investigated *in vitro* activity on bovine kidney cortex GR, which is a key enzyme that controls the cellular thiol-disulfide redox state in the cells, and essential for cellular homeostasis. Inhibition of GR may contribute to the genesis of many diseases. These three tested compounds inhibited GR (Tandogan et al. 2011).

Cholinesterase and other enzyme inhibitory activities. Activation and inhibitory effects of 3′-*O*-methylhypolaetin-7-*O*-[6‴-*O*-acetylallosyl-(1→2)-6‴-*O*-acetylglycoside] isolated from *S. libanotica* subsp. *linearis* were investigated on human cytosolic carbonic anhydrases, but the compound did not show any effect on the hCAII enzyme activity (Adem et al. 2019).

Halfon et al. (2013) investigated AChE and BChE inhibitory activities of penduletin and apigenin, isolated from the acetone extract of *S. caesarea*. While penduletin showed significant activity against BChE, apigenin showed weak activity against both enzymes.

Other studies

Seeds of *S. athoa*, *S. brevidens*, *S. caesarea*, *S. condensata*, *S. congesta*, *S. dichotoma*, *S. erythrantha var. cedretorum*, *S. germanicopolitana* subsp. *germanicopolitana*, *S. hololeuca*, *S. lanata*, *S. libanotica* subsp. *violascens*, *S. lycia*, *S. niveotomentosa*, *S. perfoliata*, *S. phrygia* and *S. pisidica* were extracted with hexane in a Soxhlet apparatus to obtain seed oils and were then analysed by GC/MS (Ertan et al. 2001). Amount of seed oils was found to be between 0.03 and 2.5 g. The major fatty acid in all species was found to be linoleic acid (between 45.4 and 64%). The oleic acid was found as the second major fatty acid in the most species (12.3–26.5%) while 6-octadecynoic acid was the second oil of *S. pisidica* and *S. caesarea*.

Dogan et al. (2010) have examined α-tocopherol, β-carotene, ferulic acid and gallic acid, total phenolic and protein contents of *S. congesta* and *S. dichotoma* beside 17 different genera using reversed-phase HPLC (RP-HPLC). *S. congesta* was found to be rich in α-tocopherol (highest 3rd plant) at 62.12 mg/100 g while *S. dichotoma* was the poorest (1.90 mg/100 g). Amount of β-carotene in *S. dichotoma* was found to be higher than *S. congesta* (2.25–0.75 mg/100 g). *S. congesta* did not include ferulic acid while *S. dichotoma* contains it at 2.50 mg/100 g. *S. dichotoma* was found fairly rich in gallic acid (22.50 mg/100 g), but not in *S. congesta* (2.50 mg/100 g). In terms of total phenolics, *S. congesta* had 3669 mg/100 g and *S. dichotoma* had 2026 mg/100 g. Protein content, which means determination of food value, of *S. dichotoma* was found higher than *S. congesta* (1478 mg/100 g, 609 mg/100 g).

In another study, the profile of heavy metal and some nutritional elements (Al, Cd, Co, Cr, Ni, P, K, Ca, S, Fe, Cu, Zn, Mn, B and Na) of *S. germanicopolitana*, *S. galatica* and *S. hispida* endemic to Turkey was detected by ICP–OES. Among the three species, *S. germanicopolitana* showed considerable variation in nutrient concentrations, but it was especially rich in iron (365 mg/kg) and potassium (2.05%). The heavy metal concentrations of all *Sideritis* species were found to be low (Korkmaz et al. 2017).

Conclusions

The Anatolian *Sideritis* species exhibited various *in vitro* and *in vivo* activities, particularly in the treatment of upper respiratory systems and anti-inflammatory/anti-ulcer disturbances and diseases. Among them, *S. congesta*, *S. condensata*, *S. trojana*,

S. perfoliata and *S. stricta* are consumed as tea and used for medicinal purposes.

Anatolian *Sideritis* species are rich in diterpenoids, flavonoid glycosides and phenylethanoid glycosides. Their essential oils are rich in monoterpenes and sesquiterpenoids, in general, particularly rich in α- and β-pinenes, which can arise to 48% of the content, followed by a sesquiterpene β-caryophyllene up to 21%.

From about 25 different Anatolian *Sideritis* species, over 40 diterpenoids, of which 35 have *ent*-kaurene skeleton, were isolated as representative secondary metabolites of the genus belonging to the Empedoclia section. Activity studies were concentrated on the extracts and diterpenic isolates and phenolic/flavonoid glycosides, including mainly antioxidant, anti-cholinesterase, anti-microbial, cytotoxic, anti-inflammatory and anti-ulcer test assays. Among the *ent*-kaurenes, 7-*epi*-candicandiol has always showed highest activity in different activity test assays including antioxidant, anti-radical, anti-cholinesterase, anti-viral, cytotoxicity and insecticidal. There are limited studies on the cytotoxic activity of *Sideritis* species. A few studies were realized on *S. lycia* extracts and constituents against a panel of cancer cell lines and Vero cells (Topcu and Goren 2007; Kilic et al. 2020) as well as antiviral and anti-inflammatory researches. Antioxidant, anti-inflammatory/anti-ulcer effects are attributed to flavonoid glycosides and phenylethanoid glycosides, in general. *S. brevibracteata*, *S. germanicopolitana*, *S. trojana* and *S. caesarea* were found to be rich in flavonoid glycosides among the studied Turkish *Sideritis* species, which displayed a variety of bioactivities. Verbascoside, as a phenylethanoid glycoside, was obtained from many *Sideritis* species, which possesses several pharmacological activities for human health, including antioxidant, anti-inflammatory, cytotoxic/anticancer and neuroprotective effects; therefore, it must be considered as a promising therapeutic agent.

In this review article, antimicrobial power of *Sideritis* species grown in Turkey was also evaluated, and antifungal activity of some *Sideritis* species was found to be much less comparable with the standard antifungal antibiotics (Dulger, Gonuz, et al. 2005; Dulger, Ugurlu, et al. 2005). The anticandidal activity of the methanol extracts of *S. dichotoma*, *S. trojana*, *S. sipylea*, *S. rubriflora*, *S. bilgerana*, *S. galatica* and *S. condensata* was searched against clotrimazole-resistant *C. albicans* (Dulger et al. 2006). Among the studied seven species, *S. trojana* and *S. bilgerana* were found to be the most active ones. Due to the strong insecticidal activities of some *Sideritis* species, such as *S. trojana* and *S. congesta*, the anticholinesterase and neuroprotective/memory enhancer activities of the *Sideritis* species should be investigated in detail by *in vitro* and *in vivo* studies.

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