



Genus *Sideritis*, section *Empedoclia* in southeastern Europe and Turkey – studies in ethnopharmacology and recent progress of biological activities

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Received: 11 October 2018 / Accepted: 8 March 2019
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Abstract

Background Over the last two decades there has been a substantial increase of the number of studies on the species of genus *Sideritis*. Species of section *Empedoclia*, occurring in the Eastern Mediterranean region and in part of Western Asia possess some remarkable characteristics and are known as valuable medicinal plants used by local people in the traditional medicine and for herbal tea. The objective of the review is to make a survey on the recent studies on the ethnopharmacology and biological activity of the species in Southeastern Europe and in Turkey, which is the center of distribution and their main occurrence.

Main body The review focuses on the ethnopharmacology and biological activities of the species of interest. The survey revealed that a total of 47 species belonging to section *Empedoclia* have been studied either in ethnopharmacological aspect, or in relation to their biological activities, or both. Most species have been used traditionally by the local people as herbal tea or for treatment of various health problems, most frequently flu, cold and respiratory diseases. *Sideritis* species demonstrate numerous biological activities and are promising for use in the therapy of many diseases and health disorders. Antioxidant activity was found in 40 species, antimicrobial and antibacterial activity – in 27 species, anti-inflammatory – in 14 species, antifungal – in 8 species, cytotoxic – in 7 species. There were also some other, more specific biological activities, found in a few species, but considered promising for further studies and application.

Short conclusion The species of genus *Sideritis*, section *Empedoclia* have been used by local people as herbal tea and in traditional medicine since long time ago. People are taking advantage of the high species diversity and are aware of their useful properties. Much more information is available on the biological activities of the target species than on their traditional uses. Most species demonstrate various biological activities and are of substantial interest for further studies on their pharmacological properties and their potential for pharmacy and medicine.

Keywords *Sideritis* · Section *Empedoclia* · Medicinal plant · Traditional use · Biological activity

Introduction

There are many examples of medicinal and aromatic plants, traditionally used since the ancient times. Their importance for contemporary life is increasingly being acknowledged. Thus, traditionally-used medicinal plants also represent a prospective source for the development of modern drugs [1]. Besides the traditional experience accumulated in the folk memory, part of which has been documented only during the last few centuries, modern-day research constantly enriches our knowledge with new information. Whereas the research results are increasingly becoming available to the scientific audience through journals and books, the experience of indigenous people in using the medicinal plants (known also as ethnomedicine or ethnobotany) is not known in details, especially in some remote areas throughout the World.

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Ethnopharmacology is a fast-developing interdisciplinary research area, which has great prospects for discovering new drugs and learning details about their use.

Southern parts of Europe are characterized by high plant diversity [2]. Medicinal plants are a part of this high diversity and the species of genus *Sideritis* are among the most popular herbs in Southeastern Europe.

According to the most recent taxonomical classification, *Sideritis* genus comprises over 150 species distributed in the Western Palearctic zone. The generic name *Sideritis* originates from the Greek „σίδηρο“, meaning iron. It is related to the use of the herb for curing wounds caused by metal arms [3].

Sideritis is taxonomically a very complicated genus, subdivided into two subgenera [4] and seven sections [3, 5–10]. Barber et al. [8] have provided evidence on the continental origin of the Macaronesian species, based on sequence data of chloroplast and nuclear markers. Recently, monophyly was tested in 19 representative species of the subgenera *Sideritis* and *Marrubiastrum* [11]. The author hypothesized that the section *Empedoclia* possibly represents an ancestral group in the genus because of the fact that its species occupy the basal branches of each main clade.

The section *Empedoclia* (Raf.) Benth. consists of perennial species, occurring in the eastern part of the Mediterranean region, in Italy, Balkan Peninsula and Asia Minor [12, 13]. From a taxonomic point of view, it is considered as very complex and the critical issues have still not been resolved completely [14–21]. According to Duman [22] there are few clear-cut species in the section. In the present review, we rely on the taxonomic treatment of Heywood [23], Duman [22], Papanikolaou and Kokkini [24], considering also the newly described species after 1982. Species number depends on the taxonomic concept, but about 90% of all species in the section occur in Turkey and about 80% of them are endemics to the country [20, 22].

The recent information revealed that most of these species have been used traditionally by people for medicinal purposes or as herbal tea. Many species of *Empedoclia* section and particularly in the Balkans are known as “Mountain tea” because they occur in the mountainous regions [25].

The objective of the present review is to summarize and compare the traditional uses of the species of genus *Sideritis*, section *Empedoclia* in Southeastern Europe and in Turkey and their biological activities established by laboratory analyses. Making this parallel is important because the traditional use of medicinal plants corresponds to the biological activities expressed and suggests the ways of their use in the modern medicine. However, looking for new activities, particularly of high-concentration extracts, poses a challenge, which is gaining momentum and these studies are getting ahead of the ethnobotanical ones.

This review highlights the potential of *Sideritis* species for the use in the traditional and modern medicine, and also

underlines the necessity of further studies to elucidate the useful properties and prospects for use of these valuable medicinal plants.

Traditional uses

According to Font Quer [26] the first information about the use of *Sideritis* species as medicinal plants dates back to the first century A.D. and was published by Dioscorides in his oeuvre “*De Materia Medica*” [27, 28]. However, it is not clear which species Dioscorides had in mind, because there are several descriptions of *Sideritis* in his book and the one corresponding to the modern *Sideritis* species is rather general. The drawings designated as *Sideritis* in a Spanish edition of *De Materia Medica* (<https://www.wdl.org/en/item/10632/>) issued by the publisher Juan Lacio, represent other species. However, this is the first mentioning of the plant in the literature. Recently, a lot of ethnobotanical studies on the use of *Sideritis* have been carried out [29–33] and they anticipated in some way the fast development of studies on the biological activities of the numerous species of the genus.

In some countries *Sideritis* species are designated by different popular names, for example, “Iron wort” in English, or “Zheleznitza” in Russian, meaning “Iron plant”. In many countries, different species are called with the common name “Mountain tea”, because most of them occur in the mountainous regions. In Albania the name is Caj Mali, in Macedonia – Sharplaninski chaj, on the Crete Island – Malotira, in Italy – Stregonia italiana, in Germany – Bergtee, or Griechischer Bergtee, in Greece – τσάι του βουνού, Olympus tea, Parnassos tea, in Slovakia – Šarplaninski Caj, in Turkey – Adaçayı and Dağçayı [25]. In Bulgaria, it is called Mursalski chai, Pirinski chai, or Alibotushki chai. Studying the popular names of plants is an important step in ethnobotanical research – it can provide information about their healing properties and value for local people (popular names, where available, are presented in Table 1). Many popular names given to a species frequently indicate its exceptional importance.

The target geographic region includes countries where preparing herbal teas at home is still very popular and even preferred – Albania, Bulgaria, Greece, Macedonia, Turkey. In most countries in Western Europe, the use of medicinal plants is based on clinically tested food supplements, drugs, extracts or isolated biologically active substances. While in Southeastern Europe people tend to collect, dry and prepare the herbs, in the countries of Western Europe people rely more on the strictly controlled herbal production standardized by pharmaceutical protocols.

Many authors in their ethnobotanical studies point out the use of *Sideritis* species as herbal tea [55, 56, 58, 76, 89, 90, 95, 129, 130]. The herbal tea or tisane of *S. raeseri* has a restorative effect [95, 99]. *S. syriaca* is used as a tonic too [77].

Table 1 *Sidertis* species and their biological activity

Species (popular name)	Country	Biological activity	References
<i>S. akmanii</i> Z. Aytac, M. Ekici & A. Donmez (Dağçayı)	Turkey	Antifeedant Anti-HIV Antibacterial	[34, 35] [36, 37] [38]
<i>S. albiflora</i> Hub.-Mor. (Yaylaçayı)	Turkey	Antimicrobial	[39–42]
<i>S. amasiaca</i> Bornm. (Tosbağa otu)	Turkey	Antioxidant	[43]
<i>S. arguta</i> Boiss & Heldr. (Eşek çayı, Donkey tea, Light Mountain tea)	Turkey	Antioxidant Anti-inflammatory	[44–46] [47]
<i>S. argyrea</i> P.H. Davis (Ezekçay, Aci çay)	Turkey	Antioxidant Antibacterial Anti-inflammatory	[43, 48] [49] [47]
<i>S. armeniaca</i> Bornm.	Turkey	Antioxidant	[50]
<i>S. athoa</i> Papanikolaou & Kokkini (Tsai tou Vounou, Greek Mountain tea)	Greece	Increase the ability to memorize	[51]
<i>S. aytacii</i> H. Duman & P. Şahin	Turkey	No data	–
<i>S. bilgerana</i> P. H. Davis (Dağçayı, Yaila çayı)	Turkey	Antioxidant Antimicrobial	[43] [31, 52]
<i>S. brevibracteata</i> P. H. Davis	Turkey	Antioxidant Antimicrobial Anti-inflammatory Antinociceptive Cancer and malaria therapy	[44, 53] [39] [44] [44] [54]
<i>S. brevidens</i> P.H. Davis (Adacayı, Ozel Cay)	Turkey	Antioxidant Antimicrobial Antifungal	[50] [40] [40]
<i>S. caesarea</i> Duman, Aytac, & Baser (Dağçayı)	Turkey	Antimicrobial Antioxidant Antiulcerogenic Antioxidative	[55] [55] [55, 56] [57]
<i>S. cilicica</i> Boiss. & Balansa (Dağçayı, Yaila çayı)	Turkey	Antioxidant Antimicrobial Antifungal	[50] [40] [40]
<i>S. clandestina</i> (Bory & Chaub.) Hayek (Greek Mountain tea)	Greece	Cytotoxic Antimicrobial Antioxidant Prevention of osteoporosis Cytotoxic Antioxidant	[34] [58, 59] [60] [61] [62]
<i>S. condensata</i> Boiss. & Heldr. (Kozali kekik, Kozali çay)	Turkey	Antimicrobial Antioxidant	[39, 63, 64] [44, 63]
<i>S. congesta</i> P.H. Davis & Hub.	Turkey	Antioxidant Diuretic Anti-inflammatory	[46, 48] [65] [47]
<i>S. dichotoma</i> Huter (Sarıkiz çayı)	Turkey	Antioxidant Antifungal	[43, 66] [31]
<i>S. erythrantha</i> Boiss. & Heldr. (Boz ot)	Turkey	Antimicrobial Antioxidant	[63, 67] [43, 48, 63, 66, 67]
<i>S. euboea</i> Heldr. (Greek Mountain tea)	Greece	Bifidogenic Cytotoxic Prevention of osteoporosis,	[68, 69] [34] [61, 70]

Table 1 (continued)

Species (popular name)	Country	Biological activity	References
		Cytotoxic	
		Protective effect on bone mineral density and strength	[71]
		Antioxidant	[69, 72]
		Antibacterial	[59]
		Alzheimer's disease	[73]
<i>S. galatica</i> Bornm. (Dağçayı)	Turkey	Alzheimer's Diseases	[74]
		Diabetes Mellitus	[74]
		Antifungal	[31]
		Antioxidant	[50, 75]
<i>S. germanicopolitana</i> Bornm. (Anadolu Dağçayı)	Turkey	Antioxidant	[50]
<i>S. gulendamiae</i> H. Duman & Karav.	Turkey	Antioxidant	[50]
<i>S. hispida</i> P. H. Davis	Turkey	—	—
<i>S. hololeuca</i> Boiss. & Heldr.	Turkey	Antimicrobial	[76]
		Antioxidant	[50]
<i>S. huber-morathii</i> Greuter & Burdet	Turkey	Antioxidant	[50]
<i>S. italica</i> (Miller) Greuter et Burdet (Stregonia italica, Stregonia siciliana, Erva i muntagna)	Italy, Sicily	Analgesic	[77]
		Anti-inflammatory	[77]
		Antibacterial	[78, 79]
		Antioxidant	[78–80]
<i>S. leptoclada</i> O. Schwarz & P.H. Davis (Kizlan çayı, Ulama out, Çay out, Kirk boğum, Anababa kokusu,)	Turkey	Antimicrobial	[41, 42]
		Antioxidant	[81]
<i>S. libanotica</i> Labill. (Altınbaş, Göktepeçayı, Anababa kokusu, Boz çay, Diken çayı)	Turkey	Antimicrobial	[76, 82]
		Increase the ability to memorize	[51]
		Cytotoxic	[83]
		Antioxidant	[43, 81, 84, 85]
		Anti-inflammatory	[47]
<i>S. lycia</i> Boiss. & Heldr. (Çayotu, Kardelen çayı, Acem arpası)	Turkey	Anti-inflammatory	[86]
		Antimicrobial	[87]
		Parkinson's disease	[88]
		Alzheimer's disease	[88]
<i>S. niveotomentosa</i> Hub.-Mor.	Turkey	Antioxidant	[50]
<i>S. ozturkii</i> Z. Aytac & Aksoy (Ada çayı)	Turkey	Anti-inflammatory	[89, 90]
		Antinociceptive	[89, 90]
		Analgesic	[89–91]
		Antioxidant	[50, 55]
		Antimicrobial	[55]
<i>S. perfoliata</i> L. (Elduran out, Kandil çayı, Ada çayı)	Greece, Cyprus, Turkey, Israel, Lebanon, Syria	Increase the ability to memorize	[51]
		Antioxidant	[92]
		Anti-inflammatory	[47, 92]
		Reducing blood pressure	[92, 93]
		Cytotoxic	[94]
		Hypoglycaemic	[93]
<i>S. phlomoides</i> Boiss. & Balansa	Turkey	Antioxidant	[50]
<i>S. phrygia</i> Bornm.	Turkey	Antioxidant	[50, 81]
<i>S. pisidica</i> Boiss. & Heldr. (Havaotu, Dalhada çayı, Eldiven çayı, Cay calbasi)	Turkey	Antimicrobial	[39]
		Anti-inflammatory	[47]

Table 1 (continued)

<i>Species</i> (popular name)	Country	Biological activity	References
<i>S. raeseri</i> Boiss. & Heldr. (Caj Mali, Mountain tea, Planinski chay)	Albania, Greece, Macedonia	Antioxidant Antimicrobial Anti-inflammatory Spasmolytic Hypotensive, vasorelaxant, cardiodepressant	[95–98] [58, 98] [96] [99] [100]
<i>S. rubriflora</i> Hub.-Mor. (Dağçayı)	Turkey	Antifungal Antifeedant	[31] [34]
<i>S. scardica</i> Griseb. (Sharplaninski chay, Pirinski chay, Mursalski chay, Alibotushki chay, Makedonski chay, Greek Mountain Tea, Olympus tea, Shepherd's tea, Τσάι του βουνού)	Albania, Bulgaria, Greece, Macedonia	Antimicrobial Antiviral (against paramyxovirus) Antifungal Anti-inflammatory Antioxidant Gastro protective ADHD – Attention-Deficit Hyperactivity Disorder Alzheimer's disease Cytotoxic Antidementive activity, Improvement of cognition Antistress	[101–103] [101] [102, 103] [102, 104] [50, 81, 97, 104–111] [104] [112] [51, 73] [104, 113–115] [116–118] [119]
<i>S. serratifolia</i> Hub.-Mor.	Turkey	Antioxidant	[50, 81]
<i>S. sipylea</i> Boiss. (Ada çayı; Ca otu, Ca şalbası, Ca şalbası)	Turkey	Antimicrobial Antioxidant	[31, 58, 120, 121] [81]
<i>S. stricta</i> Boiss. & Heldr. (Dağ çayı, Tosbağa otu)		Antimicrobial Alzheimer's disease Parkinson's disease Anti-inflammatory Analgesic	[122] [88] [88] [89, 90] [89, 90]
<i>S. syriaca</i> L. (Cretan mountain tea, Μαλοτήρας Τσαι του βουνού)	Crete, Lebanon, Syria, Turkey	Antiviral (against paramyxovirus) Antimicrobial Antioxidant	[101] [58, 101, 123] [110, 123]
<i>S. taurica</i> Stephan ex Willd.	Crimea, Bulgaria, Turkey	Antioxidant Analgesic Antiinflammatory Antiulcerogenic Antihyperglycaemic	[50] [124] [124] [124] [124]
<i>S. tmolea</i> P.H. Davis (Balbaşı, Balşalbası)	Turkey	Antioxidant	[81]
<i>S. trojana</i> Bomm (Kazdağı çayı, Sarıkızçayı)	Turkey	Antimicrobial Antimicrobial: anti-helicobacter Antifungal Insecticidal Antioxidant	[125] [126] [31] [127] [128]
<i>S. vulcanica</i> Hub.- Mor.	Turkey	Antioxidant	[50]
<i>S. vuralii</i> H. Duman & Başer	Turkey	Antioxidant Antimicrobial Antifungal	[50, 66] [40] [40]

S. condensata is used traditionally for stress relief [63] and *S. scardica* for calming down after work [131]. Apart from their usage as herbal tea, many species are used in the traditional medicine (in combination with other medicinal plants or solely) for treatment of different diseases and health problems. Lentini [132] reported using dried leaves of *S. italica* for healing wounds and about the habit of shepherds to keep some leaves in order to use them when necessary.

Below we present the main ways of traditional use of different *Sideritis* species. A schematic view is presented also in Fig. 1.

Flu and colds

The first information about the use of *S. scardica* to treat flu dates back to Dioscorides [27], the first century A.D. This is the most popular use of *Sideritis* species. *S. lycia* has been used for common cold and relief for the upper respiratory tract, due to its anti-inflammatory activity [87]. The same use was reported for *S. condensata* [63], *S. stricta* [89, 90], *S. leptoclada* [32], *S. libanotica* [133, 134] and *S. trojana* [135] in Turkey. Gürdal and Kültür [136] reported the use of *S. leptoclada* and *S. libanotica* for treatment of hoarseness and as expectorant. Hanlidou et al. [137] found that the Greek

medicinal *Sideritis* species (*S. euboea*, *S. perfoliata* subsp. *perfoliata*, *S. raeseri* subsp. *raeseri*, *S. scardica* and *S. syriaca* subsp. *syriaca*) are among the 172 taxa established in 18 medicinal plant shops in Thessaloniki, Greece. Known in the country as “Greek mountain tea”, these species are used mostly for the treatment of flu and cold, and as a diuretic and antipyretic tools [137].

Respiratory diseases

There are numerous examples concerning the favorable action of *Sideritis* species on the respiratory system. Karaman & Kocabaş [138] as well as Akbulut [139] reported the use of infusions of *S. syriaca* and *S. perfoliata*, respectively, for the treatment of chesty cough. An ethnobotanical study in Köln, Germany revealed that the Turkish immigrants use water extracts of leaves and flowers of *S. congesta*, *S. libanotica* and *S. pisidica* for the treatment of cough [30]. *S. trojana* is used for throat and chest illness [31]. An ethnobotanical survey of Inner-West Anatolia showed the uses of *S. leptoclada* as an expectorant [32]. According to an ethnobotanic study carried out by Celik et al. [140], the most used and the most widespread medicinal plant in the regions close to Mount Ida in Turkey, was the endemic species *S. trojana*. It was

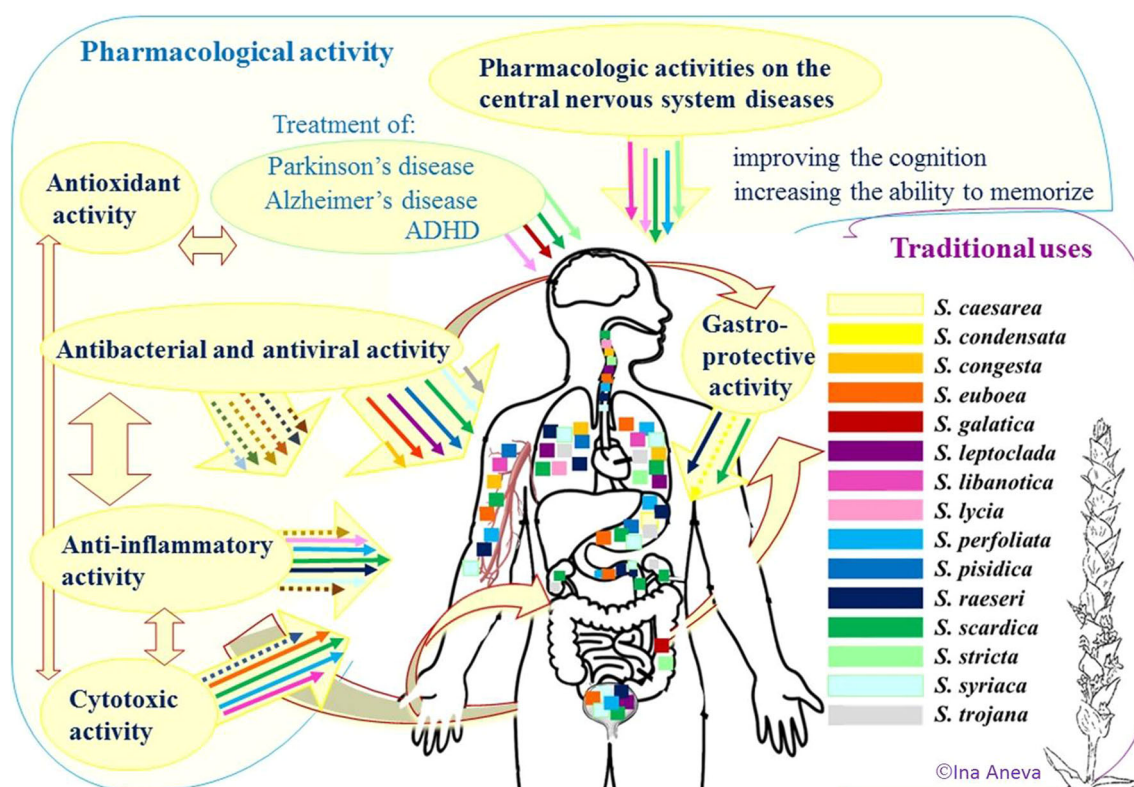


Fig. 1 Schematic illustration of traditional uses and biological activities of some *Sideritis* species. Arrows with different colors represent biological activities of different species. The species and their

corresponding color can be seen at the right part of the figure. The colors correspond also to the squares placed in the different parts of human body

recommended for treatment of sore throat and bronchitis. In the Bulgarian medical tradition, the infusions of *S. scardica* have been used mostly for treatment of diseases of the respiratory system [141]. The information available about the traditional use of *S. scardica* in Bulgaria dates back to the beginning of twentieth century. In most cases, it was published in Bulgarian in journals and books that are not easily available to the international audience. However, this information was summarized recently by Aneva [142] and Todorova & Trendafilova [33]. *S. raeseri*, also known as “mountain tea” has been widely used in the Mediterranean region as a spice and in folk medicine as a very popular decoction for cough because of its anti-inflammatory, analgesic, antitussive and antimicrobial properties [99, 143–145].

Diseases of the digestive system

S. caesarea has been widely used in folk medicine of Pinarbası (Kayseri, Turkey) for treatment of gastrointestinal disorders [56]. Everst & Öztürk [146] reported the use of *S. congesta* against obesity in the regions of Adana and Mersin in Turkey. Dulger et al. [39, 40] pointed out the uses of *S. pisidica* for abdominal pain. *S. trojana* has been traditionally used for stomach ache in Çanakkale-Turkey [135]. *S. galatica* [146] and *S. stricta* [89, 90] demonstrated carminative activity. *S. raeseri* is used in the Mediterranean region for the treatment of gastrointestinal disorders [99, 144]. The Greek species (*S. euboea*, *S. perfoliata*, *S. raeseri*, *S. scardica*, *S. syriaca*) are traditionally used for the treatment of dyspepsia, which is a result of a variety of gastrointestinal disorders [137]. *S. sipylea* and *S. tmolea* are used traditionally for the treatment of dyspepsia and diarrhea, and also in case of gallstones by the local people of Alaşehir (Manisa) in Turkey [147].

Diseases of the urinary system

Some *Sideritis* species have been used traditionally as diuretics, for example, *S. syriaca* in Turkey and *S. leptoclada* in the western part of Anatolia. Hanlidou et al. [137] pointed out the diuretic and antipyretic activities of the Greek *Sideritis*.

In Bulgaria, Dr. Alikovski [148] reported his observations about the action of water extract of *S. scardica* in the treatment of urolithiasis. He noted that the tea has a moderate diuretic effect, without irritating the kidneys, normalizing urinary pH, and acting urolitically on ureteral stones. Additionally, in the same study, *S. scardica* was reported to have favorable effect on some diseases of the male reproductive system (e.g., benign prostatic hyperplasia). Akbulut [139] reported similar application of *S. perfoliata* in the region of Adana (Southeastern Turkey). An ethnobotanical study in

Bayramiç, Çanakkale in Turkey revealed that *S. trojana* is widely used in the treatment of kidney diseases [135].

Diseases of the cardiovascular system and anemia

Pieroni et al. [30] reported the uses of *S. congesta*, *S. libanotica* and *S. pisidica* as normalizing agents for high blood pressure. In Southern Italy (Callabria) the leaves of *S. syriaca* have been used for stopping of severe bleeding [149]. Anti-anemic action has been reported for *S. euboea*, *S. perfoliata*, *S. raeseri* and *S. scardica* [99, 137, 144].

Pharmacological activity of the species of genus *Sideritis*

The literature survey of the studies on the pharmacological activity of *Sideritis* sect *Empedoclia* is summarized in Table 1.

Antimicrobial and antiviral activity

There are numerous studies proving the antimicrobial and antiviral activity of the *Sideritis* species. The information available shows that at least 19 species of section *Empedoclia* expressed antimicrobial activity. More detailed information about the species and relevant references are presented in Table 1. More specific activity was reported for several species. For example, *S. trojana* essential oil displayed moderate anti-helicobacter activity [126]. Bifidogenic activity was detected for *S. euboea* [68, 126]. According to the studies of Sattar et al. [101] all extracts expressed high antibacterial activity against *Staphylococcus aureus*. The main active substances isolated by means of thin layer chromatography were siderol, nepetalactone, and β -amirin. Oleanolic acid and its isomere – Ursolic acid – were detected for the first time in plants of genus *Sideritis*. The authors further studied in vitro the antiviral activity of extracts on four taxonomic groups, which are pathogens for humans: picorna- ortomyxo-, paramyxo- and herpes viruses. A weak activity of *S. scardica* and *S. syriaca* extracts was found against the paramyxovirus (causing conjunctivitis in humans).

Tadić et al. [102] showed that ethanol extract of *S. scardica* and its fractions (ethanol ether, ethylacetate and n-butanol) exhibit antimicrobial activity against seven strains of microorganisms – six bacteria and one fungus. The most active fraction appeared to be the one of n-butanol, acting on *Staphylococcus epidermidis*.

Extracts of six *Sideritis* species (*S. pisidica*, *S. albiflora*, *S. brevibracteata*, *S. brevidens*, *S. cilicica* and *S. vuralii*) demonstrated good antimicrobial activity against all yeasts tested

in the studies of Dulger et al. [39, 40]. High antibacterial activities of all extracts were recorded, against both gram-positive and gram-negative bacteria.

So far the only *Sideritis* species demonstrating anti-HIV activity was *S. akmanii* [36, 37]. According to the authors, the activity is due to linearol, an *ent*-kaurane diterpenoid, and such activity is also exerted by its semi-synthetic *ent*-kaurane derivatives. *Ent*-kaurane diterpenoids in *S. congesta* were studied in detail by Topçu et al. [150].

Seven species demonstrated fungicidal activity [31, 39, 40, 102, 103].

Kostadinova et al. [103] did not detect a significant activity of the hexane extracts of wild and cultivated *S. scardica* on *Escherichia coli* and *Candida albicans*, but all extracts demonstrated high activity against *Staphylococcus aureus*. High content of diterpenes and *n*-alcanes were detected in the extracts by Gas Chromatography/Mass Spectral analysis and correlation between quantitative content of diterpenes and antimicrobial activity was found.

The antibacterial activity of other *Sideritis* species was studied in detail, too. Saraç and Uğur [41] studied the effect of ethanol extracts of *S. leptoclada* and *S. albiflora* on gram-positive bacteria (*Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*). *S. leptoclada* extract had higher activity than that of *S. albiflora*. No inhibiting effect was found on gram-negative bacteria and the fungus *Candida albicans*.

Anti-inflammatory activity

Another important activity found in the studied *Sideritis* species is related to their anti-inflammatory properties. Most species demonstrated anti-inflammatory activity in different tests (see Table 1 for references), and two species (*S. brevibracteata* and *S. ozturkii*) expressed antinociceptive activity [44, 89, 90].

A large part of the substances found in *Sideritis* species possess pronounced anti-inflammatory activity. Tadić et al. [102, 104, 151] proved this activity in ethanolic extract and fractions (diethyl ether, ethyl acetate and *n*-butanol) of *S. scardica*.

Akcos et al. [86] found high anti-inflammatory activity of the phenyl-propanoid glycosides lavandulifolioside, martinolide, verbascoside and leucoseptoside A, isolated from water extracts of *S. lycia*. However, although flavonoid glycosides showed higher activity than the phenylpropanoid glycosides, the gastric ulceration effect of phenylpropanoid glycosides was lower than the one of the flavonoid glycosides.

Küpeli et al. [89, 90] found also substantial anti-inflammatory activity of acetone extract of *S. ozturkii* (17.7–28.3%), as well as of the isolated flavonoid glycosides – osteroside A, B and C (13.9–24.6%).

Anti-inflammatory activity was reported also for *S. perfoliata* [92], and *S. raeseri* subsp. *raeseri* [96]. The authors postulated that the activity was due to hypolaetin derivatives, which were abundant in the studied plants.

Menghini et al. [77] found marked anti-inflammatory activity of hexane extract from wild plants of *S. syriaca*, which, according to the authors, was related only to its apolar fraction. Güvenç et al. [44] recorded a number of biological activities in *S. brevibracteata* (see below), among them anti-inflammatory activity.

Analgesic activity was found for five species: *S. ozturkii*, *S. stricta* [89, 90], *S. syriaca* [77], *S. taurica* [124] and *S. congesta* [43].

Antioxidant activity

The most pronounced activity of *Sideritis* species and particularly of those of section *Empedoclia* is their antioxidant activity. It was found and confirmed in almost all species belonging to this section, and will probably be found in the other species, still not studied in this respect (Table 1). This is a prominent property of these medicinal plants underlining their importance and their future prospects. Together antioxidant and aldose reductase inhibitory activities were found for *S. brevibracteata* [44]. Probably the broadest study was that of Tunalier et al. [50] who studied 27 taxa (24 species and 3 subspecies) of *Sideritis*, section *Empedoclia* in Turkey, many of them for the first time. The authors classified the species according to their phenolic compounds and DPPH (2,2'-diphenyl-1-picrylhydrazil) free radical scavenging activity. A linear relationship was found between total phenol contents and antioxidant activities in the extracts.

The well-expressed antioxidant activity of *Sideritis* species is most probably due to the high content of phenolic compounds. Numerous studies were carried out with the aim of determining the anti-radical effect of different substances or of different plant extracts (prepared in different concentrations and in different solutions). The high antioxidant activity of *S. scardica* has been proven by means of different techniques [44, 50, 105–107, 152].

In their study on antioxidant activity, Koleva et al. [105] used three different methods – β -carotene bleaching test, DPPH radical scavenging method and static gas-chromatography. Most of the non-polar extracts demonstrated higher activity in BCBT (beta-carotene bleaching) test. The antioxidant activity of non-polar extracts was comparable to that of bottled hydroxytoluene, while that of polar extracts was considerably lower. Butanol, ethyl acetate and methanol extracts of *S. scardica* showed very high activity (94.1–94.4%), as tested by DPPH radical scavenging method. The activity was close to that of the rosmarinic acid (94.5%). The same method was applied to extracts of different concentrations and

the results varied from 20 to 90% [104, 108, 151]. Relatively high antioxidant activity was found by Ivancheva et al. [106] using 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid extraction method and regarding the standard 0.86 Trolox equivalent antioxidant capacity.

Nikolova & Dzhurmanski [109] and Karapandzova et al. [110] determined IC_{50} value for radical scavenging activity of *S. scardica* from Bulgarian and Macedonian localities and the results varied broadly. Nikolova et al. [152] showed that the highest antioxidant activity was expressed by 70% ethanolic extract solution. Propylene glycol extracts had 50% lower activity, and glycerin extracts showed 50% lower effect than that of propylene glycol.

No significant increase of the antioxidant activity was observed in *S. scardica* plants colonized by ectomycorrhiza with *Glomus intraradices*, while the growth and biomass were affected markedly [106].

Sagdic et al. [55] in their studies on two endemic species in Turkey – *S. ozturkii* and *S. caesarea* – confirmed the correlation between the phenolic compounds content and the level of antioxidant activity of extracts. The antioxidant activity determined by DPPH method varied within the range $41.68 \pm 1.96\%$ and $72.47 \pm 0.73\%$, depending on the concentration of phenolic compounds in the samples. Armata et al. [153] confirmed the same correlation. Different extracts (ethyl acetate, butanol, dichloromethane, diethyl ether and water) of *S. syriaca* subsp. *syriaca* showed different activities, the highest one being that of ethyl acetate extracts, where the presence of glycosides of apigenin and isoscutellarein was detected. Charami et al. [92] in their study on antioxidant and anti-inflammatory effect of extracts (methanol, ether, butanol and water) of *S. perfoliata* found that the most active compound was the acteoside (77.4%). This activity was about 20% higher than that of the control – trolox. Gabrieli et al. [95] in their study on antioxidant activity of seven isolated flavonoids of *S. raeseri* found high scavenging activity against DPPH radical of all flavonoids. Menković et al. [96] found high antioxidant and anti-inflammatory activity of ethanol extracts of the endemic subspecies *S. raeseri* subsp. *raeseri* growing in Galičica, Macedonia.

Summarizing and comparing the results of IC_{50} values of the antioxidant activities of *Sideritis* species is difficult and often misleading, due to the high variety of approaches and assays used.

Güvenç et al. [44] determined IC_{50} values of antioxidant activity in 18 *Sideritis* taxa using TBA (2-thiobarbituric acid) test. The results were highly variable ranging from 0.16 to 14.62 mg ml^{-1} . Drastic differences were recorded even between varieties of the same species [44]. The values did not allow detecting some particular trend and/or definitive conclusions. Almost all species, with a few exceptions, showed strong antioxidant activity as tested by DPPH method, and only three species expressed strong antioxidant activity when

tested with lipid peroxidation assay method (IC_{50} ranging from 0.16 to 0.33 mg ml^{-1}). Jeremic et al. [113] reported IC_{50} values ranging from 3.2 to 8.9 mg ml^{-1} in *S. scardica* and 7.6 to 12.6 mg ml^{-1} for *S. raeseri* using DPPH assay. Deveci et al. [154] used five different assays and four different variants of extracts (essential oil, hexane, acetone and methanol extracts) to study the antioxidant activity in *S. pisidica*. Methanol extract had the highest IC_{50} values among all but one (Metal chelating) of the assays applied.

Gastroprotective activity

Another important set of activities expressed by *Sideritis* species is related to their gastroprotective effect. Anti-ulcerogenic activities have been demonstrated for *S. caesarea* [55, 56] and *S. taurica* [124]. The former species was found to be protective against chemical-induced oxidative injury [57]. General gastroprotective effect was recorded for *S. scardica* [104, 151], and spasmolytic activity was documented for *S. raeseri* [99].

Tadić et al. [104, 151] found that *n*-butanol extract of *S. scardica* had the highest gastroprotective activity, exceeding the effect of the control. It was hypothesized that the activity could be due to the high phenol content in the *n*-butanol extract.

Pharmacologic activities on the central nervous system diseases

Sideritis species have also demonstrated activities related to the central nervous system. By far *Sideritis scardica* is the most studied species in this respect. It was shown to have a positive effect on Attention-Deficit Hyperactivity Disorder [112], in the treatment of cognitive impairment and improving the cognition [116–118], as well as for improvement of stress tolerance [119]. Latte [155] reviewed the use of *S. scardica* for the treatment of neurological disorders and neurodegenerative diseases. Öztürk et al. [51] proved that three species (*S. athoa*, *S. libanotica* and *S. perfoliata*) had positive effect by increasing the ability to memorize. Four species (*S. galatica*, *S. lycia*, *S. scardica* and *S. stricta*) proved effective in the treatment of Alzheimer's disease [51, 74, 88] and two (*S. lycia* and *S. stricta*) in the case of Parkinson's disease [88]. Vasilopoulou et al. [62] demonstrated that *S. clandestina* could prevent anxiety-related behavior.

Knörle [112] studied the effect of *S. scardica* extracts as inhibitors of monoamine transporters, responsible for transport of monoamines playing important role in the central nervous system (dopamine, noradrenaline and serotonin). The extracts decreased the acceptance of the three substances by increasing the active levels in the synapses, alcohol extracts

being more efficient than water ones. The extracts of *S. scardica* had higher activity in comparison with the extracts of other plant species. Traditional use of this plant in the Mediterranean region did not show lateral effects. The studies have shown that it can be used in the therapy of Attention-Deficit Hyperactivity Disorder. Öztürk et al. [51] found dose-dependent effect of extracts of *S. libanotica*, *S. perfoliata* and *S. athoa* on mice, with higher doses (500 mg kg^{-1}) making evident antistress and nervous system stimulant activities.

Cytotoxic activity

This is a relatively new field of investigation and many *Sideritis* species have demonstrated cytotoxic activity. It was found that *S. clandestina* and *S. euboea* exhibited an antiestrogenic effect on breast cancer cells without proliferative effects on cervical adenocarcinoma cells and could prevent osteoporosis [61]. The most studied species, *S. scardica* expressed clear antiproliferative activity on HCT-116 (Human colorectal carcinoma) cell line [114]. Diethyl extract of *S. scardica* at concentration 50 mg ml^{-1} exhibited the highest activity on cell line C6 (rat glioma) and the cell vitality was reduced with 59.4% [115]. The diethylether and ethyl acetate extracts of *S. scardica* caused cytotoxic effects on C6 rat glioma cells with IC_{50} $81.6 \text{ } \mu\text{g.mL}^{-1}$ and $109.4 \text{ } \mu\text{g.mL}^{-1}$, respectively [104].

The same research group found also a high cytotoxic activity of *S. scardica* extracts on B16 melanoma cell lines of mice and HL-60 human cell lines of leukemia. The extracts did not show toxicity to mononuclear cells in the peripheral blood system [113, 151]. The authors revealed that cytotoxic activity was partly due to the flavonoids found in high concentrations – apigenin and luteolin. When applied separately, these substances caused blocking of the cell cycle, apoptosis and autophagy.

Koleva et al. [156] recorded high activity of *S. scardica* extracts on the human breast adenocarcinoma cell line MCF7. The results were indicative of higher cytotoxicity of the flavonoid glycosides, as compared with phenylethanoids, towards the tested cell lines and might provide evidence on the mechanism of action of the different polyphenolics present in the aerial parts of the plant. Further researches were suggested to evaluate the possible selectivity of tested compounds towards normal cell lines.

Several other species have demonstrated cytotoxic activity, too. *S. libanotica* and *S. perfoliata* extracts were cytotoxic to several tumor cell lines [83, 94], and *S. clandestina* and *S. euboea* suppressed breast cancer cell growth [70]. Tandogan et al. [54] reported that *S. brevibracteata* inhibits bovine kidney cortex glutathione reductase in a concentration-dependent manner and therefore, could be used in cancer and malaria therapy.

Other activities

Sideritis species demonstrated also activity related to regulation of glycolytic metabolism. *S. taurica* and *S. perfoliata* expressed antihyperglycaemic and hypoglycaemic activity [93, 124], and essential oil of *S. galatica* inhibited key enzymes linked to *Diabetes Mellitus* [74]. Besides the other biological activities, *S. perfoliata* was demonstrated to reduce the blood pressure [92, 93].

Antifeedant activity is a particular property found in some species of *Sideritis*. In the course of their evolution, the plants have developed defensive mechanisms against pathogens and herbivore animals [157, 158]. Frequently, phenolic compounds play an important role in the plant defense. Since *Sideritis* species contain a lot of diverse phenolic compounds, it is expected that they could represent well-developed mechanisms of self-protection. Pronounced antifeedant activity was observed in *S. akmanii* and *S. rubriflora* [34] and insecticidal activity was found in *S. trojana* [127]. Broadening the studies probably will result in recording similar activities in many other *Sideritis* species. Generally, *Sideritis* species are considered poor in essential oil [159]. However, their chemical composition is a prerequisite for high antibacterial and antiviral activities. In most species occurring in Turkey and in Greece the essential oil contains monoterpene hydrocarbons as major constituents, and about one-third of all species are rich in sesquiterpenes [160].

Conclusions

There are about 47 species of the genus *Sideritis* section *Empedoclia* in southeastern Europe and in Turkey and almost all of them are highly valued as medicinal plants and for herbal tea across the whole region of study. Traditional use of many of these species dates back to the ancient times and the traditions were kept and developed further in the course of time. The local people used *Sideritis* species for preparing beverages like herbal tea, and also for the treatment of different diseases and health problems like flu and colds, respiratory problems, diseases of the digestive and urinary system, of the cardiovascular system, as wound healing and for some blood disorders like anemia. Most information available is about the use of *Sideritis* species in the case of cold and flu. This corresponds to the high antibacterial and antiviral activities detected in many species. These activities are supposed to be due mostly to the terpenes (diterpenes), some flavonoids, iridoids, sterols and essential oil of the target species. The traditional use of many species for treatment of digestive system diseases could be linked to the inflammatory activity, due to the flavonoids (hypolaetin, sideritoflavone, xanthomicrol).

No ethnobotanical information was found about the use of *Sideritis* species for the treatment of nervous system, although

many studies yielded interesting results and suggested new prospects for using the species in the treatment of Parkinson's and Alzheimer's diseases.

Studies of the biological activities are dominated by these focused on the antioxidant activity, followed by the ones dealing with the antibacterial activity of the extracts. This is affected by the traditional use of the plants and on the other hand, it reflects the capacities of the local laboratories and research institutions. Recently, there was a marked increase of the studies dealing with the cytotoxicity of the plant extracts. Still, the predominant studies are of screening type, with emphasis on the selecting of appropriate species, extraction method and testing material (most frequently a cell line), while the studies on the mechanism of action of the active substances are scarce.

Acknowledgements Ina Aneva expresses her thanks for the support provided by the project DFNP 17-17, Program for Career Development of Young Scientists, Bulgarian Academy of Sciences and by the Bulgarian Ministry of Education and Science under the National Research Programme "Healthy Foods for a Strong Bio-Economy and Quality of Life" approved by DCM № 577/17.08.2018. Special thanks are due to Dr. Frank O'Reilly (Agricultural & Rural Development Consultant, London) for the editing of English language.

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