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Review

Sideritis scardica Griseb., an endemic species of Balkan peninsula: Traditional uses, cultivation, chemical composition, biological activity

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ABSTRACT

Ethnopharmacological relevance: *Sideritis scardica* Griseb. is an endemic species in the Balkan Peninsula. It is used in traditional medicine as a loosening agent in bronchitis and bronchial asthma; against the common cold and lung emphysema; in the treatment of inflammation, gastrointestinal disorders and coughs; and as an active constituent of dietary supplements for the prevention of anemia. This review aims to provide a comprehensive overview of the traditional use, phytochemistry, biological activity, cultivation, and extraction of *Sideritis scardica* and to highlight the gaps in our knowledge which deserves further research.

Materials and methods: The present review is based on information collected from scientific journals, books, and electronic search. These sources include Scopus, Pubmed, Web of Science, and Google scholar as well as local books on ethnopharmacology and botany of this plant.

Results: The reported data on phytochemical studies, biological activity, cultivation, extraction, and traditional uses have been reviewed. Variability in essential oil composition of wild growing and cultivated taxa depending on ecological conditions was discussed. Flavonoids, phenylethanoids, diterpenoids, aliphatic compounds, etc. identified so far have been summarized. A comparative study on the effectiveness of different methods, solvents, and parameters of extraction has also been discussed. A broad range of activities of plant extracts and fractions as antimicrobial, anti-inflammatory, cytotoxic, antioxidant, gastroprotective, antiglioma, and triple monoamine reuptake inhibition as well as cultivation of the species as an approach for conservation of the natural habitats and provision of herb with high and permanent quality has also been presented.

Conclusions: *Sideritis scardica* has become very popular and widely advertised herb in Europe. Although some of ethnobotanical uses have been proved through *in vitro* experiments, further studies of the individual compounds or chemical class of compounds responsible for the pharmacological effects and the mechanisms of action are necessary. In addition, the toxicity and the side effects from the use of *Sideritis scardica* as well as clinical trails need attention. The variability in the chemical composition of this medicinal plant depending on the origin requires development of a protocol for its standardization. For the practice it is important to improve cultivation conditions in order to increase the accumulation of biologically active compounds and to obtain herb with permanent and good quality.

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1. Introduction

Sideritis scardica Griseb. (genus *Sideritis,* family Lamiaceae) is an endemic plant of alpine zone of the Balkan Peninsula (Heywood, 1972). It is known as Mountain tea, Ironwort, Shepard's tea, and is usually named after the mountain in which it is distributed: "Pirin tea," "Mursalski tea," or "Alibotushki tea" in Bulgaria; "Sharplaninsi chaj" in Former Yugoslav Republic of Macedonia (FYROM); or "Greek Mountain tea" and "Olympus tea" in Greece. Widely used for the treatment of inflammation, gastrointestinal disorders, and coughs, *Sideritis scardica* is also in traditional medicine as a loosening agent to combat bronchitis, bronchial asthma, the common cold, lung emphysema and as an active constituent of dietary supplements for the prevention of anemia (Đorđević et al., 1993).

During the last decade, *Sideritis scardica* from Bulgaria, FYROM, and Greece have been extensively investigated for the content of phenolic compounds, terpenoids, hydrocarbons and related compounds, and essential oil composition. It has been suggested that phenolic and/or polyphenolic components are responsible for the antioxidant activity of the alcohol extracts, while terpene components from the essential oil and diterpenoids are responsible for the anti-inflammatory, analgesic, antiulcer, antibacterial, antifungal, cytotoxic, and antitumor activities.

The aim of this review is to provide an up-to-date and comprehensive overview of the botany, conservation and cultivation, phytochemistry, traditional uses, and pharmacological activities of *Sideritis scardica.*

2. Taxonomy, morphology, and distribution

Sidertis scardica Griseb. (synonyms *Sideritis florida* Boiss. & Heldr., *Sideritis raeseri subsp. florida* (Boiss. & Heldr.) Papan. & Kokkini, *Sideritis scardica subsp. longibracteata* Papan. & Kokkini) has been placed in the *Empedoclia* (Rafin.) Benth. section (Lamioidae and Lamiaceae) (Halácsy, 1902; Papanikolaou and Kokkini, 1982; Cantino and Abu-Asab, 1994). It is a perennial herbaceous plant with a well developed root system; stems 15–40 cm high, branched and/or unbranched, and woody at base; opposite leaves with gray hairs; verticillasters many-flowered, clustered in a dense spike; middle bracts 12–20 mm long, longer than the flowers; lemon yellow glandular corolla, calyx tubular-campanulate (Assenov and Ganchev, 1978; Evstatieva, 2011). The plant reproduces mainly by seeds, but under cultivation, vegetative reproduction is possible by rhizome division (Evstatieva et al., 1990).

The distribution area of *Sideritis scardica* is closely restricted to the Central Balkan Peninsula, namely in the southwest regions of Albania, northeastern regions of Greece, central and western regions of the FYROM, the southern regions of Bulgaria (Heywood, 1972; Baden, 1991; Yordanova and Apostolova, 2000), and the European part of Turkey (Duman, 2000). The species occurs in open, dry, stony places: on limestone and on shallow and eroded soil. It grows in the subalpine and alpine vegetation belts accompanied by high-mountain, mostly hasmophytic, plants.

3. Conservation and cultivation in Bulgaria

The distribution of *Sideritis scardica* in Bulgaria is quite limited because of its intensive collection from the natural populations for years. The species is included in the threat category "endangered" on the Red list of Bulgarian vascular plants (Petrova and Vladimirov, 2009) and Red Data Book of the Republic of Bulgaria (Evstatieva, 2011), as well as in the list of medicinal plants under special regime for conservation and use. Parts of the populations are within Alibotush Strict Nature Reserve (Slavyanka Mt.), Pirin National Park, and Trigradsko Zdrelo Protected Site (Rhodope Mts.). The localities are within sites of the European Ecological Network Natura 2000 in Bulgaria. For conservation of this medicinal plant the growth biology of the species has been studied. The investigation on the main reproductive biology parameters in *Sideritis scardica* does not show strong relationship between the percentage of seed viability, seed germination, and duration of seed storage (Yankova-Tsvetkova et al., 2013), but shows its dependence on the peculiarities of the climatic conditions during the seed collection.

The field cultivation is a very important approach to protect destruction of the native populations of this endangered medicinal plant. Field cultivation involved selecting the most promising taxon in order to determine the optimal ecological conditions for sustainable growth of *Sideritis scardica* seeds collected from native populations. After germination, the plants were introduced into two experimental fields at different altitudes (550 and 1500 m. a.s.l.), and their development was monitored. The most adapted and high yielding form, "Sofia 2," was obtained, with the seeds originating from Pirin Mt. (Evstatieva, 2006). The cultivar Sofia 2 was resistant to cold (−20 °C) and relatively stable under the elevated summer temperatures of 40–45 °C. Sofia 2 was further used for plant production of horticulture in fields with different soils and climatic conditions at altitudes of 500–1500 m. a.s.l. It was observed that the quantity of the biomass increased when the plants were grown on lowland and foothill fields within the presence of highly productive soils. The optimal quantity of total phenolics and flavonoids was found both in areas with a similar climate and soil to those of native populations, as well as in the fields at an elevation of 1000 m. a.s.l. (Evstatieva and Alipieva, 2012).

In vitro culture of *Sideritis scardica* was initiated and vitamin and plant growth regulators (PGR) were modified in order to

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optimize biomass production and polyphenolics accumulation (Danova et al., 2013). PGR free medium resulted in low multiplication index and required more frequent subculture. Addition of PGR improved the biomass production with slight reduction of the proportion of flavonoids as a part of polyphenols.

4. Traditional use

Sideritis scardica is known as a healing aromatic herbal tea in traditional medicine of the Balkan countries. "Mountain tea" ("Pirin tea" or "Mursalski tea") has been used since ancient times against the broad spectrum of disorders which are summarized in Table 1. As can be seen this herb is known as an effective remedy mainly for treatment of lung diseases – cough of different origin, asthma, emphysema and bronchitis. This species is effective in treatment of disease of the prostate gland, angina pectoris, sore throat, etc. It is reported also that the tea enhances diuresis and contributes to the destruction and elimination of kidney gravel (Alikovski, 2008). "Pirin tea" was used along with other herbs as antirheumatic and immune stimulating agents. Besides as herbal tea, ethanolic extract of *Sideritis scardica* is used topically as antiseptic after tooth extraction and for oral sores. Further, leaves crushed with oil are applied as a poultice. *Sideritis scardica* is also popular as a tea of longevity in the Rhodope Mts. Pirin tea, lemon juice, and honey are traditionally used as a refreshing drink (Aneva, 2013).

In the folk medicine the tea is made from the aerial parts of the plant by infusion or decoction. Some examples for preparations and dosages are given bellow:

- Infusion of 3–5 flowering stems with 1 L of boiling water for 20–30 min, without continuous simmering. After filtering, the tea can be consumed hot or cold throughout the day (Aneva, 2013).
- One tablespoon of infusion obtained from 2 to 3 flowering stems and two cups of boiling water is taken every 2 h as warm tea (Stoyanov, 1973).
- One wineglass tea prepared by boiling of the herb (three tablespoons) in water (1 L) for 3 min is drunk three times daily instead of water before meal (Ivanov et al., 1977).
- Five grams of the herb soaked in 200 g hot water and sweetened with sugar is taken as tea (Bojchinov, 1943).
- Infusion from "Pirin tea" (2–4 sprigs) and common balm (1–2 sprigs) has to be drunk in the morning and in the evening, warmed with a little bit of sugar, and during the day it can be taken instead of water (Noev, 1932; Urumov, 1935).
- Equal amounts of *Sideritis scardica, Scolopendrium vulgare, Tussilago farfara,* pine tips, *Pimpinella anisum, Malva rotundifolia, Marrubium vulgare, Althaea alba* (roots), *Sambucus nigra* (flowers), *Foenicilum officinale, Origanum vulgare, Paliurus aculeatus, Agrimonia eupatoria, Salvia officinalis, Viola canina* (leaves), and *Glycyrrhiza glabraa* are mixed. Two tablespoons of the mixture and 0.5 L of water are boiled to remain half of the volume. Sweetened with honey is drunk as tea (Dimkov, 1979).
- Mixture of *Sideritis scardica* (10 g), *Capsella bursa-pastoris* (10 g), *Tussilago farfara* (10 g), *Hypericum perforatum* (10 g), *Urtica dioica* (15 g) and *Equisetum arvense* (10 g) is boiled in water (2 L) for 15–20 min. A wineglass of the resulting infusion should be drunk cold three times daily before meal as well as during the day instead of water (Noev, 1932).

5. Phytochemical investigations

Many chemical constituents have been identified in *Sideritis scardica*, such as essential oil components, terpenoids, flavonoids, phenolic compounds, etc.

5.1. Essential oil

Many Lamiaceae species are known to be rich in essential oils. Although the *Sideritis* species is not among them, many studies on

Table 2
Main classes of compounds in *Sideritis scardica* essential oils from different locations.

Class of compounds	Relative concentration (%)				
	Bulgaria[a,b,c]	Bulgaria[d,e]	FYROM[b,f]	Turkey[g]	Greece[h]
Monoterpenes	2.4–48.6	16.5–57.0	1.8–6.9	33.4	84.4
Oxygenated monoterpenes	0–1.6	0.1–18.1	0–30.0	24.5	5.5
Sesquiterpenes	0.2–22.2	7.3–39.7	1.3–8.6	16.4	3.1
Oxygenated sesquiterpenes	1.2–4.6	0.1–4.0	23.9–25.5	3.1	2.2
Diterpenoids	1.1–31.0	1.7–21.0	10.3–5.0	0.2	0
Others	6.2–47.6	4.1–24.4	18.1–35.7	16.7	0.4

[a] Todorova et al. (2000).
[b] Kostadinova et al. (2007).
[c] Trendafilova et al. (2013).
[d] Cultivated sample.
[e] Todorova et al. (2013).
[f] Tadić et al. (2012a).
[g] Baser et al. (1997).
[h] Kokkalou (1987).

Table 1
Traditional use of *Sideritis scardica*.

Traditional use	Reference
Asthma and cough	Davidov and Yavashev (1939), Dimkov (1979), and Ivancheva and Stantcheva (2000)
Bronchitis	Davidov and Yavashev (1939), Dimkov (1979), Ivancheva and Stantcheva (2000), and Nikolov (2006)
Lung emphysema	Urumov (1935), Petkov (1982), Ivanov et al. (1977), and Nikolov (2006)
Common cold	Ganchev (1995) and Hanlidou et al. (2004)
Angina pectoris and sore throat	Urumov (1935), Petkov (1982), and Ivanov et al. (1977)
Rhinitis	Dimkov (1979)
Diaphoretic remedy	Nikolov (2006)
Excretion of sputa	Davidov and Yavashev (1939)
Prevention of anemia	Đorđević et al. (1993) and Hanlidou et al. (2004)
Chronic kidney disease	Alikovski (2008)
Clearing the body of poisons	Alikovski (2008)
Prostate inflammation, prostatic hyperplasia, and immune stimulating	Alikovski (2008)
Antirheumatic	Noev (1932)
Wound healing, herpes, anti-septic, and anti-inflammatory	Aneva (2013)

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essential oils have been performed. As previously discussed, *Sideritis scardica* is used as a tea with a very pleasant fragrance due to the essential oil components, even despite their small concentration in the species. On the other hand, essential oil is an important characteristic for plants because of their biological activity and for chemotaxonomic purposes.

Table 2 summarizes the main classes of compounds in *Sideritis scardica* essential oil that could be found in the literature to date. More than 100 components in variable amounts were detected and identified by GC and GC/MS, belonging to monoterpene, sesquiterpene, diterpene, aliphatic and aromatic compounds. It is obvious that the oils of *Sideritis scardica* from different locations differ significantly.

Monoterpene hydrocarbons dominated the essential oil of Greek origin with α-pinene (52%) as the major one (Kokkalou, 1987). β-Pinene (17.9%), carvacrol (14.8%) and α-pinene (7.3%) have been found as main constituents in a sample of Turkish origin (Baser et al., 1997). In contrast, *Sideritis scardica* essential oils from FYROM (Kostadinova et al., 2007; Tadić et al., 2012a) were low in monoterpenes, but had a significant amount of oxygenated sesquiterpenes; α-cadinol (20.0%), a sesquiterpene alcohol, was the principal compound in the sample from Galichnik (Kostadinova et al., 2007), while hexadecanoic acid (12.9%) dominated in the population from Shara Mt (Tadić et al., 2012a). In an earlier study of Bulgarian *Sideritis scardica*, the sesquiterpenoids (β-caryophyllene and nerolidol) were found as major constituents of the oil (Todorova et al., 2000), whereas in two other oils (Kostadinova et al., 2007), the main component was octadecenol (over 20%). Further research on the essential oil composition from native Bulgarian populations revealed hydrocarbons (mono- and sesquiterpenes) as the major class of compounds, represented mainly by α-pinene (up to 25.1%) and β-pinene (up to 18.0%). Oxygenated terpenes were minor components (Trendafilova et al., 2013).

The reasons for such a big qualitative disparity among the studied oil samples could be the different plant parts (flowering tops vs. whole aerial parts), the method used for oil preparation (Likens–Nickerson vs. Clevenger type apparatuses), and different soil-climatic factors. Principal component analysis (PCA) and cluster analysis (CA) demonstrated a correlation between oil composition, altitude, and the climate of the respective natural habitats (Trendafilova et al., 2013).

A comparative study of essential oil composition of cultivar "Sofia 2" (planted in different experimental fields located at an altitude of 550–1600 m. a.s.l. and three different climatic zones) was conducted to assess the influence of these two environmental factors on it (Todorova et al., 2012, 2013). Qualitative difference in the composition of the analyzed essential oils was not observed, while the quantity of the individual components varied significantly although the initial material was the same. More common features regarding oil composition between cultivar and native taxon were found when the experimental field and native habitat were situated under the same environmental conditions.

5.2. Extracts

5.2.1. Terpenoids and aliphatic compounds

GC and GC/MS analyses of hexane extracts of wild growing and cultivated *Sideritis scardica* from Bulgaria and FYROM have been reported (Qazimi et al., 2010; Kostadinova et al., 2008; Karapandzova et al., 2013). Over 100 constituents of the extracts were identified, which belong to several classes of compounds. Diterpenes and hydrocarbons were dominantly presented in each of the studied extracts (Table 3). The main component in the Bulgarian samples was an unidentified diterpene diol monoacetate (MW 346) and with exception of one sample a high degree of similarity between all the analyzed extracts was observed. The most abundant constituents of the extracts from FYROM were two unidentified diterpene components, both with MW 286. The authors also reported seasonal variation in the content of some diterpenes and hydrocarbons.

Table 3
Main classes of compounds in *n*-hexane extracts of *Sideritis scardica* from different locations.

Class of compounds	Relative concentration (%)			
	Bulgaria[a]	Bulgaria[a,b]	FYROM[c,d]	FYROM[c,d]
Mono- and sesquiterpenoids	0–0.1	0–0.2	0.2–1.0	0.2–0.3
Diterpenoids	34.8–37.4	13.8–54.1	23.2–50.4	29.0–61.0
Triterpenoids	0	0–1.7	0.4–3.4	0.5–1.5
Sterols	–	–	0.3–6.4	1.5–4.3
Fatty acids, esters and alcohols	2.8–4.2	0.1–13.4	0.6–12.1	5.2–7.5
Hydrocarbons	37.5–42.0	24.7–58.9	18.1–48.3	13.3–42.1

[a] Kostadinova et al. (2008).
[b] Cultivated sample.
[c] Qazimi et al. (2010).
[d] Karapandzova et al. (2013).

Table 4
Main classes of compounds in *Sideritis scardica* extracts obtained by different extraction solvents and techniques.

Class of compounds	Relative concentration (%)					
	EtOH	**$(Et)_2O$**	**EtOAc**	***n*-BuOH**	**AO-CO_2**	**EO-CO_2**
Mono- and sesquiterpenoids	3.56	0.48	14.26	25.15	0.2	11.2
Diterpenoids	23.30	72.76	–	–	26.8	33.8
Fatty acids, esters and alcohols	67.75	16.72	66.48	54.59	71.1	41.2
Hydrocarbons	5.37	0.34	15.35	–	*t*	1.6

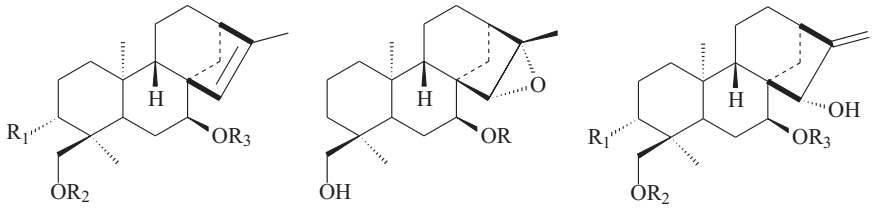
EO-CO_2 – low volatile fraction obtained by supercritical CO_2 extraction at 10 MPa and 40 °C; AO-CO_2 – fraction obtained by supercritical fluid extraction at higher pressure, 40 MPa and 40 °C (Tadić et al., 2012a), *t* – trace (percentage less than 0.01%).

Tadić et al. (2012a) evaluated the chemical profile of conventional and supercritical (SC) *Sideritis scardica* extracts and fractions obtained by successive solvent extraction using ethanol, diethyl ether, ethyl acetate, and *n*-butanol (Table 4). The results revealed significant differences in the chemical compositions of investigated extracts. It was suggested that the alternative SC CO2 extractions could not replace the conventional ones, despite the better yields of the extraction. The best extraction of diterpenes was achieved by diethyl ether (72.8%), with (*E*)-ferruginol acetate as the principle one (65.5%), while this type of compounds lacked in ethyl acetate and *n*-butanol fractions. Essential oil-like extract obtained by supercritical carbon dioxide extraction was the most abundant in fatty acids and their esters, and in diterpenes (41.8 and 33.8%, respectively).

Sideritis species were found to be rich in diterpenes (González-Burgos et al., 2011). The earliest report (Venturella and Bellino, 1979) revealed the presence of *ent*-kaurane diterpenes (Fig. 1): siderol (**1**), isolinearol (**2**), sideridiol (**3**), sideroxol (**4**), epoxysiderol (**5**), eubol (**6**), and 18-acetoxy-leucanthol (**7**) in the non-polar extract of *Sideritis scardica*, collected from Xanthi (Thrace, Greece). Further siderol was detected as a main diterpene in a sample from Bulgaria (Pirin Mt) (Taskova et al., 1997).

Recently, the quantity of siderol (**1**) and sideridiol (**3**) was determined by GC in one native population and three cultivars (Todorova, unpublished data). Siderol was the most abundant component in all of the studied petrol-ether extracts. The richest sample in these two components was the cultivar "Sofia 2" (4.6 and 0.77 mg/g, respectively), which was grown on an experimental field

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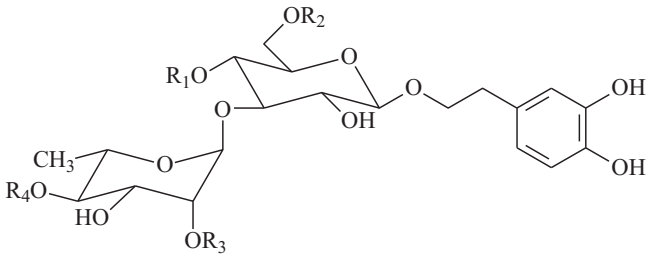


1 R_1=R_2=H, R_3=Ac
2 R_1=OH, R_2=Ac, R_3=H
3 R_1=R_2=R_3=H

4 R=H
5 R=Ac

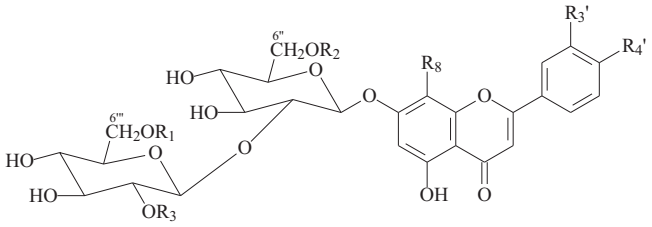
6 R_1=R_2=H, R_3=Ac
7 R_1=OH, R_2=Ac, R_3=H

Fig. 1. Diterpenoids isolated from *Sideritis scardica*.



	R_1	R_2	R_3	R_4
8	feru	glc	H	H
9	caff	api	api	H
10	caff	H	H	H
11	caff	H	H	H
12	H	caff	H	H
13	caff	H	H	api
14	feru	api	H	H
15	feru	H	H	H

Fig. 2. Structures of phenylethanoid glycosides identified in *Sideritis scardica* (feru, feruloyl; caff, caffeoyl; glc, glucose; api, apiose).



Compound	R_1	R_2	R_3	$R_{3'}$	$R_{4'}$	R_8
16	H	H	H	OH	OH	OH
17	H	H	H	H	OH	OH
18	H	H	H	H	OCH_3	OH
19	H	H	H	H	OH	OH
20	H	CH_3CO	H	H	OH	OH
21	H	CH_3CO	H	OH	OH	OH
22	CH_3CO	H	H	OH	OH	OH
23	H	CH_3CO	H	OH	OH	H
24	CH_3CO	H	H	H	OH	H
25	CH_3CO	H	H	OH	OH	H
26	CH_3CO	H	H	OH	OCH_3	H
27	CH_3CO	H	H	H	OH	OH
28	CH_3CO	H	H	CH_3O	OH	OH
29	CH_3CO	CH_3CO	H	OH	OH	H
30	CH_3CO	H	H	H	OCH_3	OH
31	CH_3CO	CH_3CO	H	OH	OH	OH
32	CH_3CO	H	H	H	OCH_3	OH
33	CH_3CO	CH_3CO	H	H	OH	OH
34	CH_3CO	CH_3CO	H	OCH_3	OH	OH
35	CH_3CO	CH_3CO	H	OH	OCH_3	OH
36	CH_3CO	CH_3CO	H	H	OCH_3	OH
37	H	H	H	OH	OH	H
38	H	H	H	OCH_3	OH	OH
39	CH_3CO	H	CH_3CO	H	OH	OH
40	CH_3CO	H	CH_3CO	OCH_3	OH	OH
41	CH_3CO	H	CH_3CO	OH	OH	OH

Fig. 3. Structures of flavonoid-7-*O*-glycosides identified in *Sideritis scardica*.

in Sofia. Their content was 50% higher in comparison to the wild growing plant from the Rhodope Mts.

The presence of triterpenoids (amyrin, ursolic, and oleanolic acids) has also been reported (Taskova et al., 1997; Karapandzova et al., 2013).

5.2.2. *Phenolic compounds and flavonoids*

Numerous phytochemical analyses were focused on the presence of flavonoids and phenolics, as the pharmacological activity of *Sideritis scardica* is partially attributed to these types of chemical compounds. Additional studies were performed to investigate the influence of eco-geographical factors on the accumulation of these biologically active secondary metabolites.

Initially, variation in the flavonoid and tannin contents of *Sideritis scardica* from wild and introduced Bulgarian populations in various plant parts depending on the seasonal ecological factors and stage of plant development were studied (Evstatieva, 2002). The maximum content of total flavonoids was observed during the budding stage (0.34%) and the lowest content – during the seed formation (0.02%), while tannins were accumulated mainly in the beginning of the vegetation (7.93%), with the lowest amount was found during the stage of full flowering (3.97%). The highest amount of flavonoids and tannins was found in the leaves and the stems, respectively.

Further investigation of *Sideritis scardica* from one natural habitat in Bulgaria (Pirin Mt, parent plant) and eight cultivated in several experimental fields (altitude 100–1500 m) exhibited the highest degree of similarity in the concentration of phenolics and flavonoids for the fields situated close to the natural habitats of the species (Evstatieva and Alipieva, 2012). The decrease of the geographical altitude led to a drop in the levels of the studied phenolic and flavonoid secondary metabolites.

Recently, the total phenol content in seven wild growing and one cultivated samples from FYROM was studied (Karapandzova et al., 2013). A similar content of total phenols ranging from 47.5 ± 0.6 to 50.8 ± 5.0 mgGA/g, regardless of the difference in location or year of collection, was found.

The occurrence of phenylethanoid glycosides (Fig. 2), acetylated and nonacetylated flavonoid-7-*O*-glycosides (Fig. 3), and hydroxycinnamic acids was investigated in *Sideritis scardica* from Bulgaria and FYROM (Table 5). The presence of two types of 8-OH flavones (hypolaetin and isoscutellarein and their methoxy derivatives) and 5,7-dihydroxy flavones (apigenin and luteolin) was found. From the chemotaxonomic point of view, phenylethanoids and monoacetylated 7-*O*-glycosides of 8-OH flavones were suggested as the most useful compounds. It should be noted, however, that significant qualitative differences were not registered. Analyses of the data revealed a strong

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Table 5
Flavonoids and phenolic compounds found in *Sideritis scardica*.

Compound	Reference
Phenylethanoid glycosides	
Echinacoside (**8**)	Petreska et al. (2011a, 2011b)
Lavandulifolioside (**9**)	Petreska et al. (2011a) and Tsibranska et al. (2011)
Verbascoside (**10**)	Petreska et al. (2011a, 2011b) and Tsibranska et al. (2011)
Forsythoside A (**11**)	Petreska et al. (2011a, 2011b)
Isoverbascoside (**12**)	Petreska et al. (2011b)
Samioside (**13**)	Petreska et al. (2011b)
Allysonoside (**14**)	Petreska et al. (2011a, 2011b)
Leucoseptoside A (**15**)	Petreska et al. (2011a, 2011b) and Tsibranska et al. (2011)
Flavonoids	
Hypolaetin 7-*O*-allosyl(1→2)glucoside (**16**)	Petreska et al. (2011a, 2011b)
Isoscutellarein 7-*O*-allosyl(1→2)glucoside (**17**)	Alipieva et al. (2010), Petreska et al. (2011a, 2011b), and Tsibranska et al. (2011)
4'-*O*-Methylisoscutellarein 7-*O*-allosyl(1→2)glucoside (**18**)	Petreska et al. (2011a, 2011b)
Apigenin 7-*O*-allosyl(1→2)glucoside (**19**)	Petreska et al. (2011a)
Isoscutellarein 7-*O*-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**20**)	Petreska et al. (2011a)
Hypolaetin 7-*O*-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**21**)	Petreska et al. (2011a)
Hypolaetin 7-*O*-[6‴-*O*-acetyl]-allosyl(1→2) glucoside (**22**)	Alipieva et al. (2010), Petreska et al. (2011a, 2011b), and Tsibranska et al. (2011)
Luteolin 7-*O*-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**23**)	Petreska et al. (2011a)
Apigenin 7-*O*-[6‴-*O*-acetyl]-allosyl(1→2)glucoside (**24**)	Petreska et al. (2011a, 2011b)
Luteolin 7-*O*-[6‴-*O*-acetyl]-allosyl(1→2)glucoside (**25**)	Petreska et al. (2011a)
Chryseriol 7-*O*-[6‴-*O*-acetyl]-allosyl(1→2)glucoside (**26**)	Petreska et al. (2011a)
Isoscutellarein 7-*O*-[6‴-*O*-acetyl]-allosyl (1→2)glucoside (**27**)	Taskova et al. (1997), Alipieva et al. (2010), Petreska et al. (2011a, 2011b), and Tsibranska et al. (2011)
3'-*O*-Methylhypolaetin 7-*O*-[6‴-*O*-acetyl]-allosyl (1→2)glucoside (**28**)	Petreska et al. (2011a, 2011b)
Luteolin 7-*O*-[6‴-*O*-acetyl]-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**29**)	Petreska et al. (2011a)
4'-*O*-Methylhypolaetin 7-*O*-[6‴-*O*-acetyl]-allosyl (1→2)glucoside (**30**)	Sattar et al. (1993), Taskova et al. (1997), Alipieva et al. (2010), Petreska et al. (2011a, 2011b), and Tsibranska et al. (2011)
Hypolaetin 7-*O*-[6‴-*O*-acetyl]-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**31**)	Petreska et al. (2011a)
4'-*O*-Methylisoscutellarein 7-*O*-[6‴-*O*-acetyl]-allosyl (1→2)glucoside (**32**)	Petreska et al. (2011a), Alipieva et al. (2010), and Tsibranska et al. (2011)
Isoscutellarein 7-*O*-[6‴-*O*-acetyl]-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**33**)	Alipieva et al. (2010), Petreska et al. (2011a, 2011b); Tsibranska et al., 2011
3'-*O*-Methylhypolaetin 7-*O*-[6‴-*O*-acetyl]-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**34**)	Petreska et al. (2011a)
4'-*O*-Methylhypolaetin 7-*O*-[6‴-*O*-acetyl]-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**35**)	Sattar et al. (1993), Taskova et al. (1997), Alipieva et al. (2010), and Petreska et al. (2011a, 2011b)
4'-*O*-Methylisoscutellarein 7-*O*-[6‴-*O*-acetyl]-allosyl-(1→2)-[6″-*O*-acetyl]-glucoside (**36**)	Petreska et al. (2011a) and Tsibranska et al. (2011)
Luteolin 7-*O*-allosyl(1→2)glucoside (**37**)	Petreska et al. (2011b)
3′-*O*-Methylhypolaetin 7-*O*-allosyl(1→2)glucoside(**38**)	Petreska et al. (2011b)
Isoscutellarein 7-*O*-[2‴,6‴-di-*O*-acetyl]-allosyl(1→2)glucoside (**39**)	Petreska et al. (2011b)
3′-*O*-Methylhypolaetin 7-*O*-[2‴,6‴-di-*O*-acetyl]-allosyl(1→2)glucoside (**40**)	Petreska et al. (2011b)
Hypolaetin 7-*O*-[2‴,6‴-di-*O*-acetyl]-allosyl(1→2)glucoside (**41**)	Petreska et al. (2011b)
Apigenin	Tadić et al. (2012)
Luteolin	Tadić et al. (2012)
Chrysoeriol	Tadić et al. (2012)
Apigenin 7-*O*-β-glucoside	Petreska et al. (2011a) and Tadić et al. (2012)
Apigenin 7-*O*-(6"-*p*-coumaroylglucoside)	Petreska et al. (2011a)
Apigenin 7-*O*-(4"-*p*-coumaroylglucoside)	Tsibranska et al. (2011) and Petreska et al. (2011a)
Luteolin-7-*O*-β-glucoside	Tadić et al. (2012)
Phenolic acids	
Protocatechuic acid	Tadić et al. (2012)
Chlorogenic acid	Alipieva et al. (2010), Tsibranska et al. (2011), and Tadić et al. (2012)
Vanillic acid	Tadić et al. (2012)
Caffeic acid	Tadić et al. (2012)
Syringic acid	Tadić et al. (2012)
p-Coumaric acid	Tadić et al. (2012)
Ferulic acid	Tadić et al. (2012)
3-Caffeoylquinic acid	Petreska et al. (2011b)
5-Caffeoylquinic acid	Petreska et al. (2011a, 2011b)
Feruloylquinic acid	Petreska et al. (2011a, 2011b)
p-Coumaric acid 4-*O*-glucoside	Petreska et al. (2011a)

similarity between all *Sideritis scardica* samples from FYROM, whereas that originated from Bulgaria was different (Petreska et al., 2011a). The latter was the richest one in total phenolic compounds. Among them phenylethanoid glycosides prevailed, followed by flavonoid acetylglycosides. Their concentration was almost two times higher in comparison with the taxa from FYROM. Isoscutellarein 7-*O*-[6‴-*O*-acetyl]-allosyl(1→2)glucoside (**27**) and 3'-*O*-methylhypolaetin 7-*O*-[6‴-*O*-acetyl]-allosyl(1→2)glucoside (**28**) – the principal flavonoid acetylglycosides reached 10.9 and 12.3 mg/g in the Bulgarian taxon. The phenolic profile of two wild and cultivated grown *Sideritis scardica* from FYROM was analyzed using water and methanol extracts (Petreska et al., 2011b). Flavonoid 7-*O*-diglycosides were not detected in the methanol extract of wild growing *Sideritis scardica*. Hypolaetin 7-*O*-allosyl(1→2)glucoside (**16**), isoscutellarein 7-*O*-allosyl(1→2)glucoside (**17**), and luteolin 7-*O*-allosyl(1→2)glucoside (**37**) were not registered in the cultivated plants. The presence of isoscutellarein 7-*O*-[2‴,6‴-di-*O*-acetyl]-allosyl(1→2)glucoside (**39**) was found only in the methanol extract from the wild growing sample.

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Acidic hydrolysis of acetone *Sideritis scardica* extracts from FYROM, and further qualitative and quantitative HPLC analysis showed the presence of isoscutellarein, chryseriol, apigenin, and 3'-methoxyhypolaetin (Janeska et al., 2007).

Quantitative analysis of total phenolics, flavonoids, and tannins in different extracts (ethanol, diethyl ether, ethyl acetate, *n*-butanol) of *Sideritis scardica* from Shara Mt. was also performed (Tadić et al., 2012). The ethyl acetate and *n*-butanolic extracts of *Sideritis scardica* were found to contain the highest amount of phenolics and flavonoids. Ferulic acid, as deduced by HPLC, was the dominant component in all investigated samples. Protocatechuic, chlorogenic, vanillic, caffeic, syringic, *p*-coumaric and ferulic acid, luteolin-7-*O*-β-glucoside, apigenin-7-*O*-β-glucoside, luteolin, chrysoeriol, and apigenin were other identified components.

Recently, the effect of extraction method – maceration, ultrasonic assisted extraction (USAE) and microwave assisted extraction (MAE), and different parameters (solvent, temperature, plant material/solvent ratio) on quantitative extraction of secondary metabolites was studied to determine the optimal conditions for extracting of flavonoids and phenolic compounds from *Sideritis scardica* (Alipieva et al., 2010). Cultivar "Sofia 2" was used as a model plant. The extraction effectiveness was evaluated by the yield of extractive, and by the yield of biologically active components: total phenolics and total flavonoids, determined spectrophotometrically; and the yield of individual flavonoids, analyzed by LC/UV-DAD/ESI-MS^n. Comparing infusion, boiling, or maceration in water, it was determined that the best way for the tea preparation was traditional infusion. The concentration of total phenols and flavonoids was the highest. Further, extraction by maceration with ethanol and water/ethanol in different proportions, and extraction kinetics were studied (Tsibranska et al., 2011). Maximum content of polyphenols and flavonoids was obtained when the H_2O/EtOH ratio was 20:80. The first 2.5 h were considered sufficient for extraction.

Regarding polyphenols and flavonoids concentration, and solvent re-use, a study on the nanofiltration of ethanolic extracts from *Sideritis* ssp. was performed (Tylkowski et al., 2011). Three membranes resistant to organic solvents were used: StarmemTM 240 (polyimide), DuramemTM 300 (modified polyimide), DuramemTM 500 (modified polyimide). The separation of flavonoids from phenols with lower molecular weight was found to be possible at molecular weight cut-off (MWCO) > 400 Da. A decrease of the flux was observed at a permeate-to-feed-volume-ratio of about 0.58, thus indicating the existence of a critical concentration, independent of the feed volume and MWCO of the membranes used. Concentrations of active compounds up to three-to-four times higher were obtained in the retentates. The extracts concentrated by nanofiltration preserved their high antioxidant activity. Further dilution of the retentates resulted in a logarithmic concentration dependence of the radical scavenging activity. The experiments suggested the possibility that permeate could be utilized in extraction, rather than ethanol; thus, the volume of the solvent can be reduced.

5.3. Mineral content

Few studies have been dedicated to the analysis of mineral content of *Sideritis scardica* from FYROM. Thus, the investigation of *Sideritis scardica* from Prilep showed the presence of macroelements Ca (12,396 mg/kg), K (10,727 mg/kg), Mg (1987 mg/kg), Na (1053 mg/kg) and Fe (455.3 mg/kg) (Žarković et al., 1993). In a recent study, *K* and Ca were the most abundant minerals in 13 samples of *Sideritis scardica* also (Karapandzova et al., 2013). The content of other macro- and microelements were represented in the following order: Mg > P > Fe > Al > Na and Zn > Mn > B > Ba > Cu > Sr > Li > Ni > Cr > Co, respectively. In all samples the concentrations of toxic elements As (0.0–0.6 mg/kg) and Pb (0.3–2.8 mg/kg) do not exceed the limits of 1 mg/kg As and 5 mg/kg Pb recommended for medicinal plants (Gasser et al., 2009), while that of Cd (0.3–3.2 mg/kg) do not correspond to the accepted limit of 1 mg/kg (WHO, 1999). Karapandzova et al. (2013) described the amount of some minerals obtained in the tea-infusion prepared from the herb. Thus, the most extractable elements were K, P, Na, Cu and Pb. Among the toxic elements, almost all amount of Pb passed into the tea-infusions and reached a concentration of 5.58 μg per cup of tea (200 mL), which is less than the FAO/WHO Provisional Tolerable Weekly Intake of 25 μg/kg body weight (WHO, 2002). Unfortunately, the authors did not report the amount of the other toxic elements Cd and As as well as that of Cu in the prepared tea-infusions in order to assess the risk for human health.

6. Biological activity

A variety of biological activities of *Sideritis scardica* have been reported: anti-inflammatory, gastroprotective, antiglioma, cytotoxic, antimicrobial, antioxidant, etc. (Table 6).

6.1. Antimicrobial activity

Hexane extracts from wild and cultivated *Sideritis scardica* samples were tested for their antimicrobial activity (Kostadinova et al., 2008). None of them was active against the gram-positive *Escherichia coli* and the fungus *Candida albicans*, but all demonstrated good activity against *Staphylococcus aureus*. None of the tested extracts differed much in their antibacterial activity; and the least active sample had the lowest concentration of diterpenes.

The ethanol extract and its ethyl ether, ethyl acetate, and *n*-butanol fractions were also examined for their antimicrobial activity using the following laboratory strains of microorganisms: *Staphylococcus epidermidis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and yeast *Candida albicans* (Tadić et al., 2007). The investigated samples exhibited antimicrobial activity of varying degrees against all the tested strains. The maximum activity was observed against *Staphylococcus epidermidis*, *Micrococcus luteus, Escherichia coli*, and *Pseudomonas aeruginosa*; and moderate activity – against *K. pneumoniae*. The *n*-ButOH fraction was the most active (50 mg/mL ethanol solution exhibited 206.7% of ampicillin activity against *S. epidermidis*).

The antibacterial activity of the CO_2-supercritical and conventional *Sideritis scardica* extracts was also investigated (Tadić et al., 2012a). Gram-positive bacteria (*Streptococcus pyogenes*, *Streptococcus canis*, *Moraxella catarrhalis*, *Streptococcus aureus*, methicillin resistant *Streptococcus aureus*, *Corynebacterium pseudotuberculosis*, *Enterococcus faecalis*), gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Pasteurella multocida* and *Haemophilus* sp.), and yeast *Candida albicans* were the tested microorganisms. Microbial susceptibility tests revealed the strong to moderate activity of all investigated extracts against the tested microorganisms (MIC from 40 to 2.56 μg/mL). Although differences in the chemical compositions (determined by GC and GC-MS analyses) were established, the displayed antimicrobial activity was similar for all the studied extracts.

6.2. Antioxidant activity

The protection against oxidative damage is one of the most widely described attributes of plant polyphenols, and is connected with their antioxidant activity. Antioxidant activity of extracts and subextracts obtained by solvents with different polarities from *Sideritis scardica* was determined by the β-carotene bleaching test (BCBT), 2,2'-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) radical scavenging method, and static headspace gas chromatography (HS-GC) (Koleva

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Table 6
Biological activities of *Sideritis scardica*.

Activity	Assay	Reference
Antimicrobial	Agar cup method	Kostadinova et al. (2008)
	Agar diffusion and broth microdilution methods	Tadić et al. (2007)
	Broth microdillution method	Tadić et al. (2012a)
Antioxidant	β-Carotene bleaching test (BCBT)	Koleva et al. (2003)
	Static headspace gas chromatography (HS-GC)	Koleva et al. (2003)
	2,2′-Diphenyl-1-picryl hydrazyl (DPPH•) radical scavenging method	Koleva et al. (2003), Tadić et al. (2008, 2012), and Karapandzova et al. (2013)
	ABTS (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)) method	Ivanova et al. (2005)
Anti-inflammatory	Carrageenan-induced rat's paw oedema test	Tadić et al. (2007, 2012)
Cytotoxic	Kenacid Blue R dye binding method	Tadić et al. (2008, 2012)
Gastroprotective	Absolute ethanol-induced stress ulcer in rats	Tadić et al. (2012)
Antiglioma	Viability of C6 rat glioma cells and rat primary astrocytes	Tadić et al. (2009) and Jeremić et al. (2013)
Triple monoamine reuptake inhibition	Rat brain synaptosome experiments and uptake experiments using JAR cells	Knörle (2012)
Influence on memory	Morris water maze	Bjoern et al. (2013)

et al., 2003). The highest antioxidant activity in the BCBT, close to that of BHT (butylated hydroxytoluene), was observed for the more apolar extracts. The inhibitory effect on β-carotene bleaching of the polar extracts and rosmarinic acid (used as a reference compound) was much lower than that of BHT. The inhibition of hexanal formation in bulk safflower oil by most of the *Sideritis scardica* extracts was as effective as BHT, but less so than rosmarinic acid. Butanol, ethyl acetate, and the total methanol extracts showed a strong radical scavenging activity against DPPH (94.1–94.4%), close to that of rosmarinic acid (94.5%).

It was also found that when the extracts were applied in the concentration range of 466.0–27.5 μg/mL, their DPPH free radical scavenging activity varied from approximately 20 to 90%, respectively, with IC_{50} values from 147.0 to 5.7 μg/mL (Tadić et al., 2008, 2012). The most active *n*-butanol extract displayed antioxidant activity comparable to positive controls (Trolox and BHT). The high total phenolic content, and the capability of the extracts tested for scavenging free radicals, might be partly responsible for both their anti-inflammatory and gastroprotective activities.

DPPH radical scavenging activity with IC_{50} values between 3.2 and 8.9 mg/mL was also found for ethanol extracts of *Sideritis scardica* from different localities of FYROM (Karapandzova et al., 2013).

Relatively high antioxidant activity [0.86 TEAC (Trolox equivalent antioxidant capacity)] of *Sideritis scardica* infusion was also determined by the ABTS (2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)) radical decolorization (Ivanova et al., 2005).

6.3. Anti-inflammatory activity

The species of the genus *Sideritis* is known in traditional medicine for their anti-inflammatory activity (González-Burgos et al., 2011). Numerous studies have validated this therapeutic indication. The ethanol extract of *Sideritis scardica*, and the diethyl ether, ethyl acetate, and *n*-butanol fractions of the crude ethanol extract, were evaluated for anti-inflammatory activity by applying the carrageenan-induced rat's paw edema test. Indometacin was used as a standard. Compared to indomethacine (4 mg/kg) which caused 50% decrease of inflammation, diethyl ether and *n*-butanol extracts exhibited almost the same effect in doses 200 and 100 mg/kg (53.6 and 48.7%; 48.4 and 49.9%, respectively) (Tadić et al., 2007, 2012).

6.4. Cytotoxic activity

The cytotoxic activity of plant extracts was assessed in PBMC, B16 melanoma, and HL-60 leukemic cells, which was then compared to the cytotoxic activity of the main phenolic compounds of extracts (Tadić et al., 2008, 2012). The diethyl ether extract showed significant dose-dependent cytotoxicity on B16 cells and HL-60 cells, as cell growth decreased to 51.3% and 77.5% of the control, respectively, when the extract was used at 100 μg/mL. It was proposed that flavonoids (apigenin, luteolin, and their corresponding glycosides) are responsible for the cytotoxic effect of diethyl ether extract. Chlorogenic acid, ferrulic acid, and chrysoeriol did not affect cell viability. Diethyl ether and *n*-butanol extracts expressed significant cytotoxic potential against HL-60 cells, decreasing their viability to 77.5% and 81.9% of the control, respectively, at a concentration of 100 μg/mL. Neither of the tested extracts nor any of the phenolic compounds showed a significant cytotoxic effect to human PBMC.

6.5. Gastroprotective activity

Different extracts of *Sideritis scardica* (diethyl ether, ethyl acetate, and *n*-butanol fractions of the crude ethanol extract) exhibited significant gastroprotective activity (Tadić et al., 2012). The most effective was the *n*-butanol extract which was even significantly more effective than ranitidine at a dose of 100 mg/kg. It was suggested that the high total phenolic content of the butanol extract was responsible for the strong gastroprotective activity.

6.6. Antiglioma activity

An investigation of the effect of *Sideritis scardica* extracts (total ethanol, diethyl ether, ethyl acetate, and *n*-butanol) on C6 rat glioma cells demonstrated that the extracts decreased the viability of treated cells to 59.4% in comparison with untreated cells (Tadić et al., 2009; Jeremić et al., 2013). The same concentrations of the studied extracts (50 μg/mL) did not change the viability of rat primary astrocytes. Extract treatment resulted in changes in cellular morphology and actin distribution in the cells. All investigated extracts increased the production of reactive oxygen species in both C6 rat glioma cells and rat primary astrocytes, as well as the caspase activation and subsequent apoptotic cell death. The diethyl ether and ethyl acetate extracts of *Sideritis scardica* displayed a cytotoxic effect on C6 rat glioma cells with IC_{50} 81.6 μg/mL and 109.4 μg/mL, respectively. The obtained cytotoxic effect was attributed to the main flavonoids in the sample apigenin and luteolin. None of the tested extracts showed significant cytotoxicity against rat astrocytes in primary culture.

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6.7. Triple monoamine reuptake inhibition

Recently, the effect of various *Sideritis scardica* extracts (water, methanol and 70% ethanol) on serotonin, noradrenalin, and dopamine uptake in rat brain synaptosomes, and serotonin uptake in human JAR cells, was studied (Knörle, 2012). It was found that all extracts inhibited the uptake of all three monoamines into rat brain synaptosomes by their respective transporters, with the alcoholic extracts being more effective than the water extract. EC_{50} values were in the range of 30–40 μg/mL. Inhibition of the human serotonin transporter by the methanol extract was even more effective (EC_{50} 1.4 μg/mL). This pharmacological property suggests that they may be useful in the phytochemical therapy of mental disorders associated with a malfunctioning monoaminergic neurotransmission, such as anxiety disorders, major depression, attention-deficit hyperactivity disorder, mental impairment, or neurodegenerative diseases.

6.8. Influence on memory

Recently the influence of *Sideritis scardica* on memorizing skills of mice in Morris water maze was studied. The authors found that the behavior testing results for mice with Alzheimer's disease treated with extract from *Sideritis scardica* vs. untreated mice correlate with the histopatological finding – reduction of total β-amyloid amount by 55% (Bjoern et al., 2013).

7. Conclusions

Sideritis scardica is a very popular and widely advertised herb in Europe. The phytochemical investigations conducted so far exhibited identification of phenolic compounds, diterpenoids and essential oil. Investigations of other classes of secondary metabolites such as triterpenoids, iridoids, lignans or coumarins are also of interest as they are biologically active compounds.

The summary of pharmacological investigations showed that they have been focused mainly on the activity of different extracts with organic solvents. However, since infusion and decoction are traditionally used, the study of aqueous extracts would be of remarkable importance. It should be noted that pharmacological studies are quite limited despite the large number of isolated individual compounds. Future research should be directed to bioguided isolation of individual compounds or chemical class of compounds responsible for the most promising pharmacological activities (anemia, kidney disease, prostate inflammation, prostatic hyperplasia, Alzheimer diseases) besides those known in the traditional medicine. In addition, the scientific verification of relation between pharmacological effects and traditional uses of *Sideritis scardica* needs further research. The toxicity and the side effects from the use of *Sideritis scardica* also have to be investigated. Clinical trials are also needed.

The so far obtained phytochemical results showed a significant variety in chemical composition of the plant material of different origins, probably depending on environmental factors, soil, altitude, etc. As a medicinal plant it is important to establish standard for the composition of *Sideritis scardica* where the presence and amount of active components to be determined. On the other hand, for medicinal purposes it is required plant material with permanent and good quality. Thus, it is important to improve cultivation conditions in order to increase the accumulation of biologically active compounds.

In conclusion, *Sideritis scardica* provides a wide range of possibilities that can be found in further scientific studies – phytochemistry, pharmacology, toxicology, pharmacognosy, agro biology, etc.

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