Assessment report on *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., herba

Draft

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

<table>
<thead>
<tr>
<th>Herbal substances (binomial scientific name of the plant, including plant part)</th>
<th><em>Sideritis scardica</em> Griseb.; <em>Sideritis clandestina</em> (Bory &amp; Chaub.) Hayek, <em>Sideritis raeseri</em> Boiss. &amp; Heldr., <em>Sideritis syriaca</em> L., herba</th>
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<td>Herbal preparation</td>
<td>Comminuted herbal substance</td>
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<td>Pharmaceutical form</td>
<td>Comminuted herbal substance as herbal tea for oral use</td>
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<td>Rapporteur</td>
<td>I. Chinou</td>
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<td>Peer-reviewer</td>
<td>B. Kroes</td>
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub) Hayek, *Sideritis raeseri* Boiss & Heldr., *Sideritis syriaca* L., herba and the draft European Union list entry on *Sideritis scardica* Griseb., herba. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no ‘overview of comments received during the public consultation’ will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph and list entry.
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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

There is not any European’s or any other existing monograph in National Pharmacopoeia or National Codex currently used in a Member State

*Sideritis* (also known as ironwort, mountain tea and shepherd’s tea) is a genus of flowering plant well known for their traditional use as aromatic herbal teas. The *Sideritis* plants are abundant in Mediterranean regions, the Balkans and the Iberian Peninsula but can also be found in Central Europe and West Asia.

*Sideritis* plants are found on rocky slopes at elevations over 1000 m which are hardy flowering perennials, while only some of the species are cultivated, among which *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek, *Sideritis raeseri* Boiss & Heldr., *Sideritis syriaca* L., in Greece and Bulgaria; otherwise, mainly the other species are harvested from the wild.

*Sideritis* (Labiatae - Lamiaceae) has been characterized as a genus with more than 150 perennial and annual vegetal species widely distributed in the Mediterranean area, together with the Canary and Madeira islands (Bojovic et al. 2011). Another author originated the genus name *Sideritis* L., from the Greek word “sideros” (iron) when used in ancient times to heal wounds caused by iron weapons (González- Burgos et al. 2011).

The plants are growing wild in the Balkan peninsula while in Greece alone, 17 different species are indigenous, extremely fragrant and very productive such as: *Sideritis athoa* (growing on Mount Athos), *Sideritis clandestina* (growing on the especially rough Mount Helmos and Taygetos in the Peloponnese), *Sideritis scardica* (on Mount Olympus), *Sideritis raeseri* (on Mount Parnassus), *Sideritis syriaca* (on the mountains of Crete, known as malotira) and *Siderities euboea* (on the mountains of the Euboea island). Among these *Sideritis raeseri*, *S. scardica*, *S. syriaca* and *S. clandestina* can be found in wild as well as cultivated.

According to Flora Europaea, all the following species of *Sideritis* species belong to Sect. EMPEDOCLIA (Rafin.) Bentham. Perrenial herbs with a woody base. Bracts entire, usually not leaf – like (Heywoood 1972).

Sect. EMPEDOCLIA comprises of the following species:

- *Sideritis syriaca* L.;
- *Sideritis clandestina* (Bory & Chaub.) Hayek;
- *Sideritis scardica* Griseb.;
- *Sideritis perfoliata* L., *Sideritis montana* L., (subsp. montana; subsp. remota);
- *Sideritis lanata* L., *Sideritis romana* L. (subsp. romana; subsp., purpurea) and *Sideritis curvidens*. [Heywoood 1972].

Geographically spread as following

- **S. scardica** Griseb.: on rocky areas and alpines regions North Greece up to Olympos mountain and Pelion mount, known also as tea of Olympos.
S. raeseri Boiss. & Heldr.: on rocky and areas of North Greece, known as tea of Velouchi and Parnassos mount.

S. syriaca L., growing wild and also cultivated in the island of Crete, known as malotira male (illness) and tirare (pull)

Sideritis clandestina (Bory & Chaub.) Hayek endemic to the South Peloponesus, in Greece.

Sideritis genus comprises of a variable species, usually divided into several species and subordinate taxa. Within restricted part of its range it is often possible to distinguish many of the local populations from each other, but when the whole range of variation is taken into consideration no satisfactory subdivision seems possible.

Sideritis syriaca L. (Cretan mountain tea); (incl. S. cretica Boiss., non L., S. raeseri Boiss & Heldr., S. sicula Ucria, S. taurica Stephan ex Willd.). Grey or white lanate perennial 10-50cm. Lower leaves 10-60 x (5-)6-20 mm, oblong to narrowly obovate, entire, crenulated or denticulate; middle and upper leaves up to 80 x 18mm, linear-lanceolate or oblong entire. Verticillasters 5-20, 6- to 10 flowered, mostly distant, rarely all crowded. Middle bracts 6-12 mm (including acumen), usually shorter than or equaling flowers, suborbicular; acumen 2-3 mm. Calyx 7-12 mm; teeth 2.5 – 5 mm, half as long to almost as long as tube. Corolla 9-15 mm yellow 2n=24 widespread in mountain rocks South Europe from Sicilia to Krym (Al, Bu, Gr, It, 9-15 mm g,Ju, Rs (K) Si. [Heywood 1972].

Sideritis clandestina (Bory & Chaub) Hayek Yellowish or grey-lanate perennial 15-40 cm. Lower leaves 25-50 x 8-20 mm, oblong-spathulate to obovate, entire or crenulated; middle and upper leaves 30-70 x 6-12 mm, linear to oblong-elliptical, entire. Verticillasters 4-20, many many flowered, crowded or to lower 1-3 distant. Middle bracts 15-25 mm (including acumen), exceeding the flowers, broadly ovate to suborbicular; acumen 4-10 mm, sparsely or densely lanate. Calyx 9-11 mm; teeth 3.5-4.5 mm, slightly shorter than tube. Corolla 10-15 mm, yellow in Mountain rocks of South Greece (Pelorponnisos) [Heywood 1972]. Plants from Taygetos (var clandestina) have a grey indumentum, linear to linear –oblong middle and upper leaves 10-20 verticillasters with the uppermost crowded and densely lanate Bracts with acumens 6-10 mm. Those of Killini (var cyllenea Heldr. Ex Boiss.) Hayek have a yellowish indumentum, oblong-elliptical middle and upper leaves, 4-10 distant verticillasters and sparcely lanate bracts with acumen 4-6 mm

Sideritis scardica Griseb is like S. clandestina [Heywood 1972] but usually densely white-lanate; lower leaves 40-80 x 6-20mm oblong-lanceolate; verticillasters crowded into a dense spike; middle bracts 12-20mm, suborbicular-cordate, sparsely lanate, abruptly acuminate with acumen 2-4 mm; calyx 9-12 mm; calyx-teeth 3-4 (~6)mm, usually about half as long as tube 2n=32 in Mountain rocks (Central part of Balkan peninsula Al, Bu, Gr, Ju) [Heywood 1972].

Analytically for Sideritis scardica Griseb. [Heywood 1972; Grisebach A. (1844): Specilegium Florae Rumelicae et Blytynae. Brunswigae, 1843-44, cited by Yaneva & Balabanski 2013]. The plant was described for the first time in Mountains of geographic area of Macedonia (Greece, FYROM, Bulgaria) in the mid- 19th century by the botanist A. Grisebach, who gave the name of the mountain, where the plant was found. The plant grows in Greece, Albania, FYROM and Bulgaria, Serbia and Turkey [Heywood 1972; Baden 1991] . Several authors have been described the species. Hardy perennial with creeping roots. Stems – in the bottom are woody, 15-50 cm tall, flower bearing stems (sprigs)-erect or prostrate, 4-angle; simple or branched (usually unbranched); Leaves – opposite, entire (smoothed) or serrated leaf blade, leaves vary by their shape: from ob lanceolate (long lanceolate), to obtuse – in the lowest veins; to longer in the middle veins; to lanceolate (linearlanceolate) - acute in the highest veins. Lower leaves have short stalk, 40-80 mm long, 6-20 mm wide. Upper leaves from the 4th vein upward are prostrate as the stalk is shortened gradually from lower to upper leaves. Bracts have
almost elliptical shape (wide heart shape at the base, acute pointed to the apex), with gentle skin consistency. When ripening they get lemon – yellow colour. In the first vein they are 38 mm long and 50-80 mm wide as to the apex of the inflorescence their dimensions decrease. Flowers are gathered in dense spike-like inflorescences, 50-80 mm long, about 30 mm wide, receptacle is tube cup-shaped, with 10 veins and 5 equal teeth, pubescent and coated by fine intertwined hairs. The whorl is yellow. With a tube hidden in the receptacle, two lipped with three-lobed lower lip. Four stamina are hidden in the tubes of the whorl. The fruit is dry, decomposed in 4 nuts. Leaves and stem are white, wooly-villous. Depending on the sea level and climate properties the plant comes out in blossom from the end of June to the beginning of September. Its smell is pleasant, and the taste is slightly bitter.

**Chemical constituents**

Terpenes, flavonoids, essential oils, iridoids, coumarins, lignans and sterols have been evaluated as chemical composition of the genus *Sideritis* with differences in the use observed among the *Sideritis* spp. and the regions where they grow depending on the plants’ properties (Bojovic et al. 2011). According to existing references, the following secondary metabolites have been isolated from Mediterranean *Sideritis* species: (Todorova & Trendafilova in 2014; Papaefstathiou et al. 2014; Vassilopoulou et al. 2013)

- **Monoterpenes**

- **Diterpenes** Many diterpenes (ent- Kaurene derivatives) have been described for *S. scardica* by the authors Venturella and Bellino, 1979 [cited in (Fraga 2012)] as isolinearol, leucanthol 18-monoacetate, siderol, sideroxol, epoxysiderol, eubol, while leucanthol 18-monoacetate has been identified as a component of *S. scardica* Griseb.

- **Sesquiterpenes**, Verbascoside, leucoscevtopside, martynoside and lavandulifolioside, ajugol, ajugoside and melittoside have been isolated from *S. scardica* (Fraga 2012)

- **Flavonoids**, Flavonoid 7-O-diglycosides, two types of flavones, 8-OH (hypolaetin and isoscutellarein and their methoxy derivatives) and 5,7-OH (apigenin and luteolin), 8-OH (hypolaetin and isoscutellarein and their methoxy derivatives) and 5,7-OH (apigenin and chryseriol); flavonoid 7-O-diglycoside; six acetylated flavonoid 7-O-diglycosides of apigenin and isoscutellarein and four isomers of apigenin 7-O-(coumaroyl) glucopyranoside together with apigenin 7-O-acetylcoumaroyl-allosyl(1 ? 2) glucoside (Bojovic et al. 2011; Yaneva & Balabanski 2013; Fraga 2012; Vassilopoulou et al. 2013; Papaefstathiou et al. 2014)

- **Triterpenes, Coumarins**

- **Sterols**, campesterol (7.6%), stigmasterol (28.4%) and β-sitosterol

- **Phenylpropanoids** hydroxycinnamic acids, phenylethanoid glycosides

- **Minerals** twenty minerals in dried over-ground parts of the plants and in water tea-infusions were determined. As most abundant the following minerals were K > Ca> Mg> P> Fe > Al > Na and microelements as well as designated toxic elements were given in the following order: Zn > Mn > B > Ba > Cu >Sr > Li >Ni> Cr > Co, and Cd> Pb > As, respectively. In case of water tea-infusions a large portion of K, P, Na, Cu and Pb, but smaller amounts of the other elements have been found (Bojovic et al. 2011; Yaneva & Balabanski 2013).
Especially, the investigation of in S. scardica, and S. raeseri revealed the presence of a complex profile of hydroxycinnamic acids, phenylethanoid glycosides and both acetylated and non acetylated flavonoid 7-O-glycosides. Two types of flavones, 8-OH (hypolaetin and isoscuttellarein and their methoxy derivatives) and 5,7-OH (apigenin and luteolin), have been confirmed. All the flavonoid glycosides detected were 7-O-alsosyl-(1,2)-glucoside derivatives, 5,8-di hydroxyflavones with a different substitution in the B-ring. Differences in the phenolic profile of hydroxycinnamic acid and flavonoid 7-O-glycosides were found between S. scardica and S. raeseri. Flavonoid 7-O-diglycosides were not detected in the methanol extract of Sideritis scardica (Bojovic et al. 2011). The identification of the flavonoids in populations of S. scardica and S. raeseri in central Balkan region (Former Yugoslavian Republic Of Macedonia, FYROM) and the presence of two types of flavones, 8-OH (hypolaetin and isoscuttellarein and their methoxy derivatives) and 5,7-OH (apigenin and chryseriol), have been confirmed, and the possibility of distinguishing between the two studied species (S. scardica and S. raeseri) has been suggested (Janeska et al. in Bojovic et al. 2011). Verbascoside, leucosceptoside, martynoside and lavandulifolioside were determined to be the most important compounds with respect to their pharmacological properties (Ertan et al. 2001, Ezer et al. 1992; Pinar et al. 2004; Rodriguez et al. 2000 all cited in BOJOVIC et al. 2011) Especially, the investigation of the FYROM’s Sideritis species (S. scardica, S. raeseri) illustrated the presence of a complex profile of hydroxycinnamic acids, phenylethanoid glycosides and both acetylated and non acetylated flavonoid 7-O-glycosides. Two types of flavones, 8-OH (hypolaetin and isoscuttellarein and their methoxy derivatives) and 5,7-OH (apigenin and luteolin), have been confirmed.

Many diterpenes (ent-kaurene derivatives) have been described for S. scardica by Fraga 2012 as isolineolar, leucanthol 18-monoacetate, siderol, sideroxol, epoxysiderol, eubol, while leucanthol 18-monoacetate has been identified as a component of S. scardica Gris. which grows in the central part of the Balkan Peninsula Coumarins and other aromatic derivatives such as the verbascoside, leucosophdeside A and tentatively, forsytheside A, allosylsiderol and echinacoside, have been identified as components of S. raeseri Boiss. et Heldr. and S. scardica L. from FYROM (Petreska et al., 2011; Koleva et al., 2003; also cited in Fraga 2012).

An evaluation with detailed information by Todorova and Tredafilova in 2014, of Sideritis scardica Sideritis raeseri Boiss and Heldr., from Greece, Bulgaria and FYROM, and its content of phenolic compounds, terpenoids, hydrocarbons and related compounds, as well as essential oil composition was published (Todorova & Tredafilova 2014; Petreska et al. 2011; Janeska et al. 2007; Kostadinova et al. 2007; cited also by Yaneva & Balabanski 2013. For S. scardica the first phytochemical analysis was performed by Bojchinov (Bojchinov, A. Pharmacognostic study of Sideritis scardica Griseb, Aptekearski pregled, 1943, 9, 151-158 (in Bulgarian) cited by Yaneva & Balabanski 2013).

In a recent study (Vassiliopoulou et al. 2013) the phytochemical composition of herbal tea from Sideritis clandesta (Bory & Chaub.) Hayek was monitored. The phytochemical profile of the S. clandesta tea was determined by liquid chromatography-UV diode array coupled to ion-trap mass spectrometry with electrospray ionization interface. The identified compounds were classified into several natural product classes: quinic acid derivatives, iridoids, phenylethanol glycosides and flavonoids. The LC/DAD/ESI-MSn analysis of the aqueous extract led to the separation and identification of the majority of the extract components, seventeen in total, which belonged to several classes of secondary metabolites: quinic acid, melittoside, phenylpropanoids and flavonoid derivatives. Specifically, two quinic acid derivatives along with two melittoside derivatives, two phenylethanoid glycosides (b-hydroxyverbascoside or b-hydroxyisoverbascoside is described for the first time in Sideritis species) and one flavonoid 7-O-diglycoside were identified along with six acetylated flavonoid 7-O-diglycosides of apigenin and isocuttellarein and four isomers of apigenin 7-O-(coumaroyl) glucopyranoside. Among the aforementioned compounds, the main constituents in the extract were
found to be melittoside and quinic acid derivatives. Apigenin 7-O-acetylcoumaroyl- allosyl glucoside was identified and was characterized in the extract for the first time. Moreover, the chemical profile of S. raeseri was found comparable with previous studied Sideritis species. Nine 7-o-allosyl glucosides of 5,8-dihydroxy substituted flavones were isolated from a fraction of the methanol extract of the aerial parts of Sideritis raeseri Boiss et Heldr. subsp. raeseri. (Gabrieli, et al. 2015), as well as with S. syriaca (Kogiannou et al. 2013)

Very recently, the metabolic profiling of six different Sideritis species growing in Greece (south Balkan peninsula): S. clandestina subsp. clandestina, S euboea, S. perfoliata subsp. perfoliata, S. raeseri subsp. raeseri, S. scardica and S. syriaca (Papaefstathiou et al. 2014) were compared (through HPTLC platform, and in LTQ Orbitrab HRLC-MS. It was revealed that the water extracts of the plants were containing the same secondary metabolites. Only limited quantitative differences were observed between them. In more details, the water extract of S. euboea was similar to that of S. clandestine, S. scardica, S. raeseri and S. perfoliata. In contrary S. syriaca presented significant quantitative differences (only quantitative) with all previous referred Sideritis species. Similar results were given comparing the chemical profiles of all ethanol extracts (15%, 30% and 70%) of the six selected Sideritis species. Phytochemical investigation led to the isolation of the major components which were identified and structurally determined as acteoside, martynoside, and glycosides of apigenin, hypolaetin, isosculetarein, 4'-O-methylisoscutelarein and 4'-'-O-methyl-hypolaetin. Moreover, the total phenol content revealed that all extracts possessed high content in phenolic compounds (ranging from 82-140 mg GAE/g of extract) (Papaefstathiou et al. 2014)

**Essential oil of Sideritis species**

The essential oil of S. scardica (0.03%) contained mainly of beta-pinene (17.9%); carvacrol (14.8%) and a-pinene (Fraga 2012) while in another study al. (Kostadinova et al. 2007) reported that the essential oils of the species Sideritis scardica and Sideritis raeseri from Bulgaria and FYROM consisted of diterpenes. The oil of S. raeseri had higher concentrations of sesquiterpenes and as main components germacrone (25%) and elemol acetate (15.9%) have been determined, (Bankova et al., 1996; and Bruno et al., 2005; cited in Kostandinova et al. 2007; Bojovic et al. 2011).

- Herbal preparation(s)
  The monograph describes the uses of the comminuted herbal substance.
  - Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

This monograph refers Sideritis scardica Griseb.; Sideritis clandestina(Bory & Chaub) Hayek , S. raeseri Boiss & Heldr., Sideritis syriaca L.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

### 1.2. Search and assessment methodology

Search terms: Sideritis; Sideritis scardica Griseb.; Sideritis clandestina(Bory & Chaub) Hayek , S. raeseri Boiss & Heldr., Sideritis syriaca L.; Mountain tea, Sideritis herba

Databases: Pubmed, Medline, HealLink, Scopus.
2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

There are no registered or authorised medicinal products in the EU / EEA Member States

Information on medicinal products marketed in the EU/EEA

No registered medicinal products in the EU/EEA

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

No combination medicinal products containing Sideritis are marketed in the EU

2.1.2. Information on products on the market outside the EU/EEA

Use in Albania

There are 4 Sideritis species used in Albania; (Sideritis scardica Griseb.; Sideritis clandestina (Bory & Chaub) Hayek, S. raeseri Boiss & Heldr., Sideritis syriaca L.). S. scardica is used in Albania traditional as tea (bulk ware) and in recent times by modern tea packages as single portion (product: Cai mali alcaj with 1-1.5 g/cup water 150mL; www.alcaj.com May 2014)

A medicinal-ethnobotanical study in Albania confirmed the way as bulk ware in local markets as well pharmaceutical stores. Main use is the abdominal pain (stomach ache) and against sore throat by viral infections (Rexhepi et al. 2013). Because wild collection of the raw material is dominant, the species S. scardica as well S. raiseri are often used parallel. It is used in Albanian folk medicine as a relaxation, during bronchitis and bronchial asthma, against colds and lung emphysema (UNDP report 2006 - Caji I malit).

2.2. Information on documented medicinal use and historical data from literature

Sideritis, is an herb belonging to a large genus in the family of Labiatae. The plant was known to ancient Greeks, also from Theophrastus. Although Dioscorides in De Materia Medica describes three Sideritis species, only one (probably S. scordioides) is thought to relate to Sideritis botanical genus. In ancient times Sideritis was a generic reference for plants capable of healing wounds caused by iron weapons during battles.
The name "sideritis" (ironwort) derives from the Greek word for iron, "σίδηρος" (SEE-thee-ros) literally translated as "he who is or has the iron", because sideritis was considered a great "remedy against trauma from iron weapons," that is to say wounds of war in ancient times. Dioscorides advises the herbal infusion of "mountain tea" to soldiers as a rejuvenating, regenerating aid to help them heal quicker and fuller (González-Burgos et al. 2011).

In Crete, under the Venetian rule, sideritis-iron wort (Sideritis syriaca) gained another name, popular to this day on the island and throughout the world: malotira (μαλοτήρα). This name derives from the Italian: male means ailment/illness, while tirare means to pull, to draw out. Malotira draws out the illness. As in Crete, the common name for Mountain Tea is "malotira", almost in every region of Greece has its own name for the brew, such as "Olympos tea," and "Parnassos tea," reflecting the name of the mountain where it grows.

The most common English name other than Mountain Tea is "Shepherd's Tea," because Greek shepherds would use the plants to make a brewed tea while tending their flocks high in the hills. Indeed sideritis (and malotira) are pleasant herbal remedies for a sore throat, a great aid in any disease of the respiratory system, possessing soothing and healing properties, as well as a healing cure for ailments of the digestive tract.

**Parts used**


**History of the use**

*Sideritis scardica* Griseb

Very popular in Greece, Bulgaria, Albania and FYROM, the plant is used as a herb either for the preparation of herbal teas, or for its aromatic properties in local cuisines. The herbal tea is commonly prepared by decoction, by boiling the stems, leaves and flowers in a pot of water, then often serving with honey and lemon. Mountain tea has been traditionally used to aid digestion, strengthen the immune system and suppress common cold, the flu and other viruses, allergies and shortness of breath, sinus congestion, even pain and mild anxiety. Significant research has been done on mountain tea confirming its popular use to prevent colds, flu, and allergies. Most of this research has taken place in universities in the Netherlands and in Greece, Turkey, FYROM, Bulgaria, and Albania, where the plants are indigenous.

**Other names**: Various names have been attributed to the plant in the ancient world, among them the name
○ Sidertis scardica Griseb. (genus Sideritis, family Lamiaceae) – internat. accepted name (database PlantList 2014: [http://www.theplantlist.org/tpl/record/kew-191627](http://www.theplantlist.org/tpl/record/kew-191627)) Common known as “Mountain tea”, “Greek Mountain tea” and “Olympus tea” however in different regions linked to different species. Greece: Ελληνικό Τσάι του βουνού (Greek Mountain tea)

○ Albania: Caj Mali

○ Bulgaria: Mursalski Tee, Pirinski Tee or “Alibotushkitea”

○ FYROM: Планински чай (Planinski Tea)

○ England/UK: Greek Mountain Shephard’s Tea

○ Austria: Püringertee

○ Germany: Griechischer Bergtee (Greek Mountain tea), Griechisches Eisenkraut (Greek Ironworth)

○ Russia: Железница (Greek Ironworth)

In a recently published review (Todorova & Trendafilova 2014) the perennial herbaceous plant Sidertis scardica Griseb. (syn= Sideritis florida Boiss. & Heldr., Sideritis raeseri subsp. florida (Boiss. & Heldr.) Papan & Kokkini, Sideritis scardica subsp. longibracteata Papan. & Kokkini) has been qualified as an endemic species of the Balkan peninsula traditionally used as a healing aromatic herbal tea in the traditional medicine of the Balkan countries. Different names are used like Mountain tea, Ironwort, Shepard’s tea, and due to its regional origin it is named Pirin tea,” “Mursalski tea,” or “Alibotushkitea” in Bulgaria, “Sharpla-ninsci chaj” in Former Yugoslav Republic of Macedonia (FYROM) or “Greek Mountain tea” and “Olympus tea” in Greece (Todorova & Trendafilova 2014). In the traditional medicine Mountain tea” (“Pirin tea” or “Mursalski tea”) has been used mainly for the therapy of lung diseases like cough of different origin, asthma, lung emphysema and bronchitis. Furthermore, it is reported that Sidertis scardica is traditionally helpful for the treatment of inflammation, gastrointestinal disorders, and common cold and as dietary supplement for the prevention of anemia ((Đorđević et al., 1993), cited in (Todorova & Trendafilova 2014)). The author Alikovski, 2008, cited in this overview reported about treatment of the prostate gland, angina pectoris, sore throat, and enhancement of diuresis as well as of the elimination of kidney gravel when the tea of this species is used. It has also been described that “Pirin tea” was used together with other herbs as antirheumatic and immune stimulating agents and that tea is prepared from the aerial parts of the plant by infusion or decoction.

In written documents was pointed out the use of Sidertis scardica (mountain tea) in Bulgaria as a herbal tea and in the traditional medicine . In written sources dated from the first decades of the last century the so called in Bulgaria Pirin mountain tea in the folk medicine was recommended as tea that is “aromatic and healing” in the treatment of respiratory diseases; in cough, asthma, bronchitis and for favourable effects on the respiratory organs “You can heal yourself. Heal yourself with herbs. Book 1st, author and editor Ivan Karamitrev, "Modern publishing house, Plovdiv, 1934, p. 67, №17 Pirin tea. cited by Yaneva & Balabanski 2013 ; in common cold, ,( Flora of the People’s Republic of Bulgaria, Under the edition of the Academician D. Jordanov, Sofia, 1989, vol., p 371.275 ; cited by Yaneva & Balabanski 2013); it helps relieve symptoms of cough, bronchitis, common cold, sputum expectoration; cough of different origin (bronchitis, emphysema) (Stoyanov, Neno. Our medicinal
In addition to the traditional use as tea the species *Sideritis scardica* ethanolic extracts are topically administered as antiseptic after tooth extraction and for oral sores and crushed leaves with oil for the use as a poultice.

The aerial parts of "mountain tea" are traditionally known for their anti-inflammatory, antimicrobial, and gastro-protective properties (Bojovic et al. 2011). Moreover, according to the author Petreska et al., 2011b, the distribution of *S. scardica* extends on Greece, FYROM, Bulgaria, Southwest Albania as well as on Turkey. Thus, the Greece mountain tea or Greece Ironwort are based on the species *Sideritis scardica* having become popular and particularly appreciated as relaxing tea after daily work. The following trade names defined correctly under the botanical name *Sideritis scardica* Griseb. are listed: as Greek Mountain tee in Greece, CajMali in Albania, Mursalski tea or Pirinski tea in Bulgaria, Planinski tea in FYROM, Greek Mountain or Shepard’s Tea, Püringer Tee in Austria and Griechischer Bergtee or Griechisches Eisenkraut in Germany [Govaerts 2003; cited in (Feistel 2013)].

Infusions of aerial parts of *S. scardica* are used in Bulgaria traditionally as expectorant for the treatment of pulmonary emphysema and angina pectoris (Ivancheva and Stantcheva, 2000; cited in Gonzalez-Burgos et al. 2011). *S. scardica* is also described for the relief of bronchitis and bronchial asthma and against the common cold and lung emphysema, as well as widely used for the therapy of inflammation, gastrointestinal disorders and coughs and as an active constituent of dietary supplements for the prevention of anaemia [(Dordeviae et al., 1993; cited in Bojovic et al. 2011). All biological activities previously cited in the literature have been mainly attributed to the phenolic and terpenoid content of this plant (Petreska et al., 2011; cited in Bojovic et al. 2011).

*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub) Hayek , *S. raeseri* Boiss & Heldr., *Sideritis syriaca* L., in Greece

- Mountain Tea is very popular in Greece. It is in use for its positive effect for colds, respiratory problems and digestion. It is also used as an anti-inflammatory and to reduce fever.
- In Greece, it is sold in bulk in pharmacies, herb-and-spice shops, or it can be picked fresh and dried at home. Outside Greece, it is sold as "Greek Mountain Tea," or "Greek Mountain Shepherd’s Tea," at specialty shops.

**Information on period of medicinal use in the European Union**

**Herbal Use**

Very popular in Greece, Albania, Bulgaria and FYROM, the plant is used as a herb for the preparation of herbal teas. The herbal tea is commonly prepared by decoction, by boiling the stems, leaves and flowers in a pot of water, then often serving with honey and lemon. Mountain tea has been traditionally
used to aid digestion, strengthen the immune system and suppress common cold, the flu and other viruses, allergies and shortness of breath, sinus congestion, even pain and mild anxiety.

Most of this research has taken place in universities in Greece, Bulgaria, Turkey, FYROM, and Albania, where the plants are indigenous

**Use in Greece:**

*S. syriaca, S. scardica, S. raeseri and S. clandestina* which are also cultivated are in use since ancient times as tea (bulk ware); the plant is used as a herb either for the preparation of herbal tea prepared by decoction, by boiling the stems, leaves and flowers in a pot of water.

15-25 g of the dried leaves and flowers /approx. 1 liter of boiling water (rd. 0.95 liter)

It is used for colds, respiratory problems, digestion, the immune system, mild anxiety as herbal tea for the treatment of inflammations, coughs and gastrointestinal disorders. In Greece, it is sold in pharmacies, herb-and-spice shops, or it can be picked fresh and dried at home. [http://greekfood.about.com/od/mezethesdrinks/a/tsaitouvounou.htm](http://greekfood.about.com/od/mezethesdrinks/a/tsaitouvounou.htm) may 2014 The enormously popular in Greece leads constantly increasing the area for cultivation (Goliaris A. 1998) of *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub) Hayek and *S. raeseri* Boiss & Heldr., and *Sideritis syriaca* L.,

The mountain tea in Greece (mainly *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub) Hayek, *S. raeseri* Boiss & Heldr., *Sideritis syriaca* L., and other only growing wild Sideritis species) is a herbal tea of exceptional quality, taste, aroma. Traditionally has been used for its beneficial effects on the stomach, as tonic, as diuretic and as detoxification agent. The decoction of the aerial parts has been used of colds and infections of the upper respiratory system and for digestion. In combination with cinnamon and honey properties that are enhanced with the addition of honey. Even considered good as respiratory, as anti-irritant and as antianemic because its content in Fe (Floca et al 1981, cited in Raptou 2011).

**Use in Bulgaria**

It was reported by Aneva that: 4 species of Herba *Sideritis* are endemic according to Flora Republic of Bulgaria1989 (*S. lanata, S.montana, S. syriaca, and S.scardica*). For *Sideritis scardica* the traditional use as herbal medicine is described is a mucus-reducing and soothing agent for coughs and bronchitis (Aneva 2013).

Stoyanov delivered in **1960** the first written source about the use of three *Sideritis* species (*S. montana, S. taurica and S. scardica*) as tea. Tea was mainly used as bulk ware a traded in special food shops / herbal shops near the origin area of growing or in pharmacies. Aneva IY 2013 described the traditional use of *Sideritis scardica* in Bulgaria in detail. “Tea of longevity” is the name in the Rhodope mountain.

Decoctions or infusions of the aerial part are used as antioxidant, anti-inflammatory, antimicrobial, vulnerary, analgesic, carminative and anti-ulcerative agents.”(Aneva 2013).
These herbal teas were used since ancient times to combat the negative effects of asthma and bronchitis, and as a cough suppressant (Davidov et al., 1939: Materials for Bulgarian botanical dictionary; summarized in English in Todorova and Trendafilova 2014).

Dr. Alikowski from Bulgaria has published to books (in Bulgarian language only) concerning “Mursalski tea”; 1st circulation in 1999, updated in 2008. (Alikowski 2008) It was reported that “Mursalski Tea” is also appropriate for treating chronic kidney disease. As the tea causes a change of pH in the urine, it enhances diuresis and contributes to the destruction and elimination of kidney gravel.

Todorova and Trendafilova, 2014, describes that the herbal tea is recommended to be used by infusing it with boiling water for 20 to 30 minutes, without continuous simmering. After filtering, the tea can be consumed hot or cold throughout the day.

Three to five flowering stems (approx. 4 g each) 12-20g are necessary for one liter of tea. The large range in traditional dosage goes back to the use of raw material in bulk, means small bouquets on flowering stems.

Infusion 3-4 g of sprigs are cut and 2 cups of boiling water (300-400 ml) are added. After 10 minutes the infusion is drained and 1 table spoon is taken every 2 hours. Always it should be drunk as warm tea in separate sips (Stoyanov, Neno. Our medicinal plants, part II, Sofia, Nauka I Izjustvo, 1973, pp 396-398 Cited in Yaneva & Balabanski 2013). in colds;

Decoction • 3 table spoons of the herb are boiled in 1 l water for 3 minutes.
One glass of wine of the decoction is drunk up to 3 times daily, instead of water before meal. The herb has pleasant scent and in winter it can be taken as tea (Ivanov, I., I. Landzhev, G. Neshev. Herbs in Bulgaria and their use. Printing house “Zemizdat”, Sofia, 1977, pp 213-214 Cited in Yaneva & Balabanski 2013.).

Infusion 3–4 g, soaked in 200 g hot water, sweetened with sugar and having light brown-reddish colour and with pleasant scent and tasty to be drunk as tea several times (2-3 times) daily (Bojchinov, A. Pharmacognostic study of Sideritis scardica Griseb, Aptekarski pregled, 1943, 9, 151-158 (in Bulgarian). Cited in Yaneva & Balabanski 2013).

The plant Pirin tea (Sideritis scardica Griseb.) has been placed in the List of medicinal plants (herbs index) that is regulated under the Medicinal Plants Act, published in State Gazette, No. 29 as of April 7, 2000 in Bulgaria.

The main effects that characterize the plant in different diseases are: expectorant, alleviating in inflamed mucous membranes of the respiratory system, antitussive, anti-inflammatory (in diseases of the respiratory system and rheumatism); anti-asthmatic. Cited in Yaneva & Balabanski 2013.

**Extract preparations of Sideritis scardica in Bulgaria**

- In addition to the traditional use as tea, Sideritis scardica ethanolic extracts are topically administered as antiseptic after tooth extraction and for oral sores and crushed leaves with oil for the use as a poultice

Different tea applications as "greek mountain tea" are on the market as bulk ware for cough and colds are also marketed in Germany.
According to the overview of the European market, there are no registered/authorised herbal preparations containing on the market. However according to references listed below, in the Balkan peninsula (Greece, Turkey, Bulgaria, Albania; Serbia, FYROM etc) Sideritis herba is widely in medicinal use since at least the last 40 years (in accordance with existing references).

Therefore for Sideritis herba a period of at least 30 years of medicinal use, as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is fulfilled. The evidence on traditional medicinal use is confirmed by a large number of publications providing consistent information.

**Literature:**

The monograph describes the use of the comminuted herbal substance as a herbal tea (infusion, decoction) for oral use.

Table 1: Overview of historical data

<table>
<thead>
<tr>
<th>Herbal preparation</th>
<th>Documented use / traditional use</th>
<th>Pharmaceutical form</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Sideritis scardica</em> herba</td>
<td>expectorant, alleviating in inflamed mucous membranes of the respiratory system, antitussive, sweat reducing</td>
<td>Infusion – 3-4 g, soaked in 200 g hot water to be drunk as tea, several times daily</td>
<td>Aptekarski pregled, 1943, 9, 151-158 (in Bulgarian). Cited in Yaneva &amp; Balabanski 2013</td>
</tr>
<tr>
<td><em>S. montana, S. taurica S. scardica; S. raeseri; S. syriaca</em></td>
<td>For relief of cough associated with cold</td>
<td>3-5 g of sprigs are cut and 2 cups of boiling water (300-400 ml) are added. After 10 minutes the infusion is drained and 1 table spoon is taken every 2 hours. Always it should be drunk as warm tea in separate sips</td>
<td>Zemizdat”, Sofia, 1977, pp 213-214 Cited in Yaneva &amp; Balabanski 2013 Stoyanov, Neno. Our medicinal plants , part II, Sofia, Nauka 1 Izjustvo, 1973, pp 396-398 Cited in Yaneva &amp; Balabanski 2013 Davidov et al., 1939: Materials for Bulgarian botanical dictionary; summarized in english in TODOROVA 2014 Đorðeviæ et al., 1993 Ivancheva and Stantcheva, 2000 Alikovski, 2008 Todorova &amp; Trendafilova 2014</td>
</tr>
<tr>
<td><em>Sideritis scardica</em> herba</td>
<td>relieve symptoms of cough, bronchitis, common cold, sputum</td>
<td>Infusion 2-5 g of the dried leaves and flowers in</td>
<td></td>
</tr>
</tbody>
</table>

Assessment report on *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., herba

EMA/HMPC/39455/2015
## 2.3. Overall conclusions on medicinal use

The indications recommended in the monograph:

1. Traditional herbal medicinal product used for the relief of cough associated with cold.
2. Traditional herbal medicinal product used for the relief of mild gastrointestinal disorders.

### Posology

**Adults and elderly**

Indication 1) and 2)

- Single dose: Herbal tea: 2-4 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion, 3 times daily.
- Daily dose: 12 g

The use in children and adolescents under 18 years of age is not recommended.

### Duration of use

**Indication 1)**

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

**Indication 2)**

If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

### Table 2: Overview of evidence on period of medicinal use

<table>
<thead>
<tr>
<th>Herbal preparation</th>
<th>Indication</th>
<th>Posology, Strength</th>
<th>Period of medicinal use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal preparation</td>
<td>Indication</td>
<td>Posology, Strength</td>
<td>Period of medicinal use</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------</td>
<td>------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Sideritis scardica herba</td>
<td>expectorant, alleviating in inflamed mucous membranes of the respiratory system</td>
<td>Infusion – 5 g, soaked in 200 g hot water to be drunk as tea, several times daily (proposed up to 3-4 times)</td>
<td>Aptekarski pregled, 1943, 9, 151-158 (in Bulgarian). Cited in Yaneva &amp; Balabanski 2013</td>
</tr>
<tr>
<td>S. montana, S. taurica S. scardica; S. raeseri; S. syriaca</td>
<td>For relief of cough associated with cold; to aid digestion</td>
<td>3-4 (3-4 g) sprigs are cut and 2 cups of boiling water (300-400 ml) are added. After 10 minutes the infusion is drained and 1 tablespoon is taken every 2 hours. Always it should be drunk as warm tea in separate sips</td>
<td>Zemizdat&quot;, Sofia, 1977, pp 213-214 Cited in Yaneva &amp; Balabanski 2013 Stoyanov, Neno. Our medicinal plants, part II, Sofia, Nauka I Izjustvo, 1973, pp 396-398 Cited in Yaneva &amp; Balabanski 2013 Davidov et al., 1939: Materials for Bulgarian botanical dictionary; summarized in english in TODOROVA 2014 Đorđević et al., 1993 Ivancheva and Stantcheva, 2000 Alikovski, 2008 Todorova &amp; Trendafilova 2014</td>
</tr>
</tbody>
</table>

### 3. Non-Clinical Data

#### 3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

#### 3.1.1. Primary pharmacodynamics

**Antimicrobial activity**

A recent review publication (Todorova & Trendafilova 2014) summarizes the data of the antimicrobial activity of *Sideritis scardica* (ethanol extract and its ethyl-ether, ethyl-acetate, and n-butanol fractions) (Tadić et al., 2007, cited in Todorova & Trendafilova 2014). Antimicrobial activity of varying degrees against *Staphylococcus epidermidis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and yeast *Candida albicans* has been demonstrated. Maximum activity was observed against *Staphylococcus epidermidis*, *Micrococcus luteus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, moderate activity against *K. pneumonia* and the most active one against *S. epidermidis* was the extract of 50mg/mL ethanol solution comparable to 206.7% of ampicillin activity. *Sideritis scardica* Griseb has been investigated (Tadić et al. 2012) also for its antimicrobial properties against Gram-positive bacteria, *Streptococcus pyogenes*, *Streptococcus canis*,...
Moraxella catarrhalis, Staphylococcus aureus, methicillin resistant Staphylococcus aureus, Corynebacterium pseudotuberculosis, Enterococcus faecalis, Gram-negative bacteria Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Pasteurella multocida and Haemophilus sp., and yeast Candida albicans. As a result, it can be concluded that the minimal inhibitory concentration values (MIC values from 40 to 2,560 μg/mL) of the investigated extracts indicated antibacterial activity of the investigated S. scardica extracts against the tested microorganisms. The investigators concluded that the different types of terpenoids could contribute for this antibacterial activity (Tadic et al. 2012).

It has been established that extracts from Sideritis scardica, Sideritis syriaca and Sideritis montana /extracted with organic solutions/ showed a strong activity against Staphylococcus aureus, and butanol extract of Sideritis syriaca exhibited anti-yeast activity versus C. albicans (Cited in Yaneva & Balabanski 2013).

In vivo experiments

**In vivo anxiolytic-like behavioral and antioxidant properties**

Another study (Vassilopoulou et al. 2013) monitored the effect of drinking of herbal tea from Sideritis clandestina for 6 weeks on behavioral and oxidant/antioxidant parameters of adult male mice and also to evaluate its phytochemical composition.

The phytochemical profile of the Sideritis tea was determined by LC-UV diode array coupled to ion-trap mass spectrometry with electrospray ionization interface. The effects of two doses of the herbal infusion (2 and 4% w/v, daily) intake on anxiety-like state in mice were studied by the assessment of their thigmotactic behavior. The oxidant/antioxidant status of brain (-Ce), liver and heart of adult male Balb-c mice following the consumption of Sideritis tea was also evaluated via the measurement of malondialdehyde (MDA) and reduced glutathione (GSH) levels using fluorometric assays. The study was further extended to determine the antioxidant effects of the herbal tea on specific brain regions (cerebral cortex, cerebellum and midbrain). The identified compounds were classified into several natural product classes: quinic acid derivatives, iridoi ds, phenylethanol glycosides and flavonoids. The results showed that only the 4% Sideritis tea exhibited anxiolytic-like properties as evidenced by statistically significant (p < 0.05) decrease in the thigmotaxis time and increase in the number of entries to the central zone in comparison with the control group. Consumption of both tea doses (2 and 4% w/v) elevated GSH (12 and 28%, respectively, p < 0.05) and decreased MDA (16 and 29%, p < 0.05) levels in brain (-Ce), while liver and heart remained unaffected. In regard to the effect of herbal tea drinking (2 and 4% w/v) on specific brain regions, it caused a significant increase in GSH of cerebellum (13 and 36%, respectively, p < 0.05) and midbrain (17 and 36%, p < 0.05). Similarly, MDA levels were decreased in cerebellum (45 and 79%, respectively, p < 0.05) and midbrain (50 and 63%, respectively, p < 0.05), whereas cerebral cortex remained unaffected. In conclusions the water extract (infusion) of mountain tea drinking prevents anxiety-related behaviors and confers antioxidant protection to rodent's tissues in a region-specific, dose-dependent manner, and its phytochemical constituents are shown for the first time (Vassilopoulou et al. 2013)

**In vivo Gastro protective and anti-inflammatory activities**

S. scardica, mountain tea, samples were tested (Tadic et al. 2012) as ethanol, diethyl ether, ethyl acetate and as n-butanol extracts of the crude ethanol extract for their anti-inflammatory activity and gastroprotective activities. Investigated extracts dissolved in DMSO, and were administered p.o. in doses of 50–200mg/kg 60min prior to ethanol. Ranitidine given in doses of 5–20mg/kg p.o. was used...
as a reference drug. Compared to the effect of the positive control, the anti-inflammatory drug indomethacin (4mg/kg), which produced a 50% decrease in inflammation, diethyl ether and n-butanol extracts exhibited about the same effect in doses of 200 and 100 mg/kg (53.6 and 48.7%; 48.4 and 49.9%, respectively). All investigated extracts produced dose-dependent gastroprotective activity with the efficacy comparable to that of the reference drug ranitidine. The reduction of the rat paw edema was reached by the doses of 100 and 200 mg/kg and the level was comparable to the positive control, indomethacin, which was administered in a dose of 4mg/kg producing 50% reduction.

**Spasmyolytic activity**

In a study, the effects of an ethanol extract of *S. raeseri* on intestinal activity were investigated. Air-dried and powdered aerial parts were extracted with 96% ethanol. The rat ileum preparations were incubated in Tyrode's solution gassed (95% O₂/5% CO₂) at 37°C. The ethanol extract of *S. raeseri* (0.03-0.3 mg/mL) relaxed spontaneous contractions in isolated rat ileum, similar to that produced by papaverine. The plant extract in a concentration-dependent manner (0.015-0.15 mg/mL) significantly inhibited the contractile response to acetylcholine (P<.01). A relaxation-inducing effect of the *S. raeseri* extract was observed on the precontracted ileum by histamine and barium chloride. Plant extract (0.03-0.3 mg/mL) significantly shifted the histamine concentration-response curve to the right and down (P<.01). The *S. raeseri* extract (0.03-0.3 mg/mL) significantly inhibited the contractions induced by barium chloride (P<.01). The results show that the ethanol extract of *S. raeseri* can produce inhibition of the spontaneous rat ileum contractions and contractions induced by different spasmyogens. These data indicate that *S. raeseri* acts as a spasmyolytic on intestinal smooth muscle, which supports its use in gastrointestinal disorders (Brankovic et al. 2011)

Table 3: Overview of the main non-clinical data/conclusions

<table>
<thead>
<tr>
<th>Herbal preparation tested</th>
<th>Posology</th>
<th>Experimental model</th>
<th>Reference</th>
<th>Main non-clinical conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Sideritis scardica</em></td>
<td>Ethanol extracts</td>
<td><em>In vitro</em></td>
<td>Tadić et al., 2007; Todorova &amp; Trendafilova 2014</td>
<td><strong>Antimicrobial activity against S epidermidis, M. luteus, E coli, P aeruginosa</strong>, moderate activity against K. pneumonia the extract of 50mg/mL ethanol solution was the most active against <em>S. epidermidis</em> comparable to 206.7% ampicillin activity</td>
</tr>
<tr>
<td><em>Sideritis syriaca</em></td>
<td>butanol extract of <em>Sideritis syriaca</em></td>
<td><em>In vitro</em></td>
<td>Yaneva &amp; Balabanski 2013</td>
<td>anti-yeast activity versus C. albicans</td>
</tr>
<tr>
<td><em>Sideritis scardica, Sideritis syriaca and Sideritis montana</em></td>
<td>Ethanol and water extracts</td>
<td><em>In vitro</em></td>
<td>Tadić et al. 2012</td>
<td>MIC values from 40 to 2,560 μg/mL <em>S pyogenes</em>, S</td>
</tr>
<tr>
<td>Herbal preparation tested</td>
<td>Posology</td>
<td>Experimental model</td>
<td>Reference</td>
<td>Main non-clinical conclusions</td>
</tr>
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</tr>
<tr>
<td><em>S. raeseri</em></td>
<td>ethanolic extract</td>
<td><em>in-vitro</em></td>
<td>Tadic et al. 2012</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; values between 7.6 - 12.6 mg/mL.</td>
</tr>
<tr>
<td><em>Sideritis clandestina</em></td>
<td>Water extracts (infusions drinkable)</td>
<td><em>In vivo</em></td>
<td>Vassilopoulos et al. 2013</td>
<td>4% Sideritis tea exhibited anxiolytic-like properties as evidenced by statistically significant (p &lt; 0.05) decrease in the thigmotaxis time and increase in the number of entries to the central zone in comparison with the control group</td>
</tr>
<tr>
<td><em>Sideritis scardica</em></td>
<td>Butanol extract</td>
<td><em>In vivo</em></td>
<td>Tadic et al. 2012</td>
<td>The butanolic extract showed high protection against the ulcerogenic effect by the use of ethanol at an oral dose 100 mg/kg comparable with the control of ranitidine.</td>
</tr>
<tr>
<td><em>Sideritis raeseri</em></td>
<td>Ethanol extract</td>
<td><em>In vivo</em></td>
<td>Brankovic et al. 2011</td>
<td>The ethanol extract of <em>S. raeseri</em> (0.03-0.3 mg/mL) relaxed spontaneous contractions in isolated rat ileum, similar to that produced by papaverine</td>
</tr>
</tbody>
</table>
3.1.2. Secondary pharmacodynamics

Antioxidant activity

Plant samples from several species and populations of the genus *Sideritis* grown in Bulgaria (*S. scardica, S syriaca* and *S montana*) were tested for their antioxidant activities by the β-carotene bleaching test (BCBT), 2,2′-diphenyl-1-picrylhydrazyl (DPPH•) radical scavenging method and static headspace gas chromatography (HS-GC) and compared with the antioxidant activity of two reference compounds of different polarity, butylated hydroxytoluene (BHT) and rosmarinic acid. The highest antioxidant activity in the BCBT, close to that of BHT, was observed for the more apolar extracts. The inhibitory effect on β-carotene bleaching of the polar extracts and rosmarinic acid was much lower than that of BHT. The inhibition of hexanal formation in bulk safflower oil by most of *S syriaca* and *S scardica* extracts was as effective as BHT but less so than rosmarinic acid. Extracts from butanol and from ethyl acetate and the total methanol extracts from all *Sideritis* plants studied showed a strong radical scavenging activity against DPPH•, close to that of rosmarinic acid. *S montana* extracts were, as a whole, slightly weaker radical inhibitors than the extracts from the other two species (Koleva et al. 2003; Karapandzova et al. 2013). In another study *S. scardica*, was tested (Tadic et al. 2012) (ethanol, diethyl ether, ethyl acetate and as n-butanol extracts) for their antioxidant activity and showed that the ethyl ether extract of *S. scardica* revealed the highest anti-inflammatory effect. In another in-vitro study (Danesi et al. 2013) the authors compared the antioxidant activity of *Sideritis scardica* to a *Camellia sinensis* (CS) extract in the biological system (HepG2 cells) against oxidative stress. Under control conditions, after the induction of oxidative stress, and compared to the CS extract as well as to the antioxidant α-tocopherol (TC) the results did not show significant differences between both extracts. For *Sideritis scardica* the authors identified a lower phenolic concentration and a smaller total antioxidant capacity than the CS extract; however, cellular antioxidant effects in the test system were similar for both extracts. The publication of Petreska and coworkers (Petreska et al. 2011a) addresses the phytochemical evaluation and the related antioxidant activity as well as the dietary burden of phenolics by a cup of domestic infusion of *Sideritis* ("Mountain tea"). It has been analyzed that the total phenolic content for *Sideritis* was around 190 mg when a 2 g infusion bag was used in case of the methanol extracts, and it was about 72 mg in water extracts. As a result, the methanol extract of *S. raeseri* (wild growing) demonstrated the highest antioxidant capacity as shown by DPPH, ABTS and FRAP assays and the antioxidant activity was linearly correlated with phenolic content. In another study (Papaefstathiou et al. 2014) the free radical (DPPH) were studied on six different *Sideritis* species growing in Greece (south Balkan peninsula): *S. clandestina subsp. clandestina, S euboea, S. perfoliata subsp. perfoliata, S. raeseri subsp. raeseri, S. scardica* and *S. syriaca* The scavenging assays revealed that all extracts possessed significant antioxidant activity (% inhibition >74 at 300μg/ml)

Antiglioma activity

Todorova & Trendafilova (2014) summarized the effects on C6 rat glioma cells when the *Sideritis scardica* extracts (ethanol, diethylether, ethylacetate, and n-butanol) have been applied. The extracts decreased the viability of the C6 rat glioma to 59.4% compared to the untreated cells. The viability of the rat primary astrocytes was not impacted negatively by the same extracts concentrations used (50 μg/mL) but the cellular morphology and actin distribution were damaged. It has been reported that the four extracts increased the production of reactive oxygen species in C6 rat glioma cells, the rat primary astrocytes, as well as the caspase activation and subsequent apoptotic cell death. The diethylether and ethylacetate extracts caused cytotoxic effects on C6 rat glioma cells with IC50 81.6 μg/mL and 109.4 μg/mL, respectively. The main flavonoids like apigenin and luteolin have been made responsible for the
cytotoxic effects on the C6 rat glioma cells. No cytotoxicity against rat astrocytes in primary culture could be found by the use of the extracts.

Different extracts of the aerial parts of *Sideritis scardica* have been investigated on the reuptake of serotonin, dopamine and noradrenaline in rat brain synaptosomes. The in-vitro study has been performed according to the method of Perovic and Müller, 1995; as cited by the authors of the present investigation (Feistel & Appel 2013). Together with [3H]-serotonin, [3H]-dopamin or [3H]-noradrenalin the rat synaptosomes were incubated with increasing concentrations of the extracts. As positive controls imipramin (serotonin), GBR 12909 (dopamin) und protriptylin (noradrenalin) have been implemented. At a dosage of 100mg *Sideritis scardica* ethanolic extract/kg bw similar spectral changes were observed compared to the *Rhodiola rosea* root extract in the same dosage. Main effects seen were a significant attenuation of alpha2 waves followed by decreases in spectral theta power in the fronto cortex and hippocampus. Similar spectral changes have been found after the administration of 1mg/kg paroxetine, a synthetic antidepressive drug and methylphenidate. The author suggested that the *Sideritis scardica* herb might be regarded as an up to now unknown substitute of the class of adaptogens with possible psychostimulant and antidepressive effects and might be in accordance with the findings of Knoerle, 2012) who reported about the inhibition of the re-uptake of serotonin, dopamine and noradrenaline. In conclusion, the tested extracts of *Rhodiola* and *Sideritis* revealed similar frequency patterns comparable to a psychostimulant drug (methylphenidate) as well to the antidepressive drug (paroxetine).

**Cytotoxic activities**

Ethanol, diethyl ether, ethyl acetate and n-butanol extracts *S. scardica*, were tested for their cytotoxic potential. (Tadic et al. 2012) For the evaluation of cytotoxic potential of the different extracts PBMC, B16 melanoma, and HL-60 leukemic cells were used and compared to the cytotoxic activity of the main phenolic compounds of the extracts. Only diethyl ether extract caused significant dose-dependent cytotoxicity in B16 cells and HL-60 cells, decreasing cell growth to 51.3% and 77.5% of control, respectively, when used at 100μg/mL. The most cytotoxic compounds were Iuteolin, apigenin-7-O-β-glycoside, apigenin, and luteolin-7-O-β-glycoside.

**Influence on memory**

The authors Todorova and Trendafilova (Todorova & Trendafilova 2014) gave recently summary among other issues of the biological activity of *Sideritis scardica* Griseb. They presented the results of *Sideritis scardica* on memorizing skills of mice in the Morris water maze experiment. The results revealed that the behavior testing of mice with Alzheimer’s disease when treated with extract from *Sideritis scardica* compared to untreated mice show a reduction of total α-amyloid amount by 55%.

**Triple monoamine re-uptake inhibitors**

Knoerle 2012 demonstrated that water and alcoholic extracts of *S. scardica* inhibited the serotonin, noradrenaline and dopamine uptake in rat brain synaptosomes and additionally the serotonin uptake in human JAR cells (placental choriocarcinoma cells). The uptake of all three monoamine transporters was influenced in a concentration-dependent manner. The alcoholic extracts were more effective than the water extract when tested in rat brain synaptosomes with EC50 values of about 30–40 μg/ml. In case of the human serotonin transporter it has been shown that the methanol extract was more effective (EC50 1.4 μg/ml) than the inhibition of the rat brain serotonin transporter. The author suggested that among others, terpenes, flavonoids and phenols could be responsible for the effects on the CNS activity. And concluded that the tested *S. scardica* extracts could be used for the prevention and treatment of anxiety disorders, major depression, attention-deficit hyperactivity disorder, mental impairment or neurodegenerative diseases.
3.1.3. Safety pharmacology

No data

3.1.4. Pharmacodynamic interactions

None reported

3.1.5. Conclusions

*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub) Hayek, *S. raeseri* Boiss & Heldr., *Sideritis syriaca* L., have been described as endemic species of the Balkan traditionally used as healing aromatic herbal teas in folk medicine of the Balkan countries since centuries and consumption have been described mainly for the therapy of lung diseases like cough of different origin, asthma, lung emphysema and bronchitis. Furthermore, it is reported that *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub) Hayek, *S. raeseri* Boiss & Heldr., *Sideritis syriaca* L., are helpful and supportive based on traditional knowledge for the relief of cough associated with cold, also used for relief of mild gastrointestinal disorders. Pharmacological properties of the plant found in relevant scientific literature like the antimicrobial activities make the traditional use in uncomplicated disorders of the lung plausible.

The published data referring to the indications and preparations are limited, but existing data on the above-mentioned pharmacological activities support the plausibility for the traditional use, for relief of cough associated with cold, of *Sideritis* herba. Moreover the traditionally known use of the plant against gastrointestinal disorders is considered in the knowledge of the results from an *in vitro* test of a n-butanol extract investigated by Tadic et al. 2012 the anti-inflammatory, gastro protective and spasmolytic activities with positive final outcome. The data indicate that *Sideritis species* act potentially as spasmolytic on intestinal smooth muscle, which supports its use in gastrointestinal disorders (Brankovic et al. 2011).

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

**Pharmacokinetic data**

By *in vivo* studies, several phenolics belonging to *Sideritis* species like flavones and hydroxycinnamic acids have been studied with regards to their absorption and metabolization by the human gastrointestinal tract and following occurrence at systemic level in plasma and excretion by urine (Meyer et al., 2006; Lafay et al., 2008; Jia et al., 2009; all cited in Petreska et al. 2011a).

Regarding the *in vivo* experiments with animals and clinical trials with humans, it can be concluded that the flavones apigenin, luteolin and scutellarein are absorbed but at low rate (around 0.25% of the initial intake). They are extensively conjugated to glucuronides, sulphates and transformed to methylated forms (Meyer et al., 2006; Lafay et al., 2008; Jia et al., 2009; Hanske et al., 2009; all cited in Petreska et al. 2011a). 3-caffeoylquinic acid and 5-caffeoylquinic acid are assumed to be directly absorbed in the stomach, hydrolyzed by enterocytes at the small intestine and absorbed by the caecal microflora as caffeic acid (Lafay et al., 2006; Lafay et al., 2008; cited in Petreska et al. 2011a). The authors summarized that the most abundant phenolics by domestic infusion (boiling water) were...
esterified forms of flavones and hydroxycinnamic acids and the preparation of a tea should consist of 60% of leaf and 40% of flower, decreasing up to the maximum the addition of stem.

The metabolites were characterized as hypolaetin, methylhypolaetin, isoscutellarein, methylisoscutellarein, and apigenin and 32 phenolic acid metabolites. The authors reported about the urinary excretion of polyphenol metabolites which corresponded to 5% (n/a) of the intake of polyphenols by the decoction. The most abundant flavonoid metabolites in urine samples were analyzed to be of 87-94% of the total polyphenolic metabolites content. Mostly methylhypolatein and methylisoscutellarein glucuronides have been found as metabolites. The urinary excretion of isoscutellarein was evaluated as 10 times higher than that of hypolaetin and apigenin showed high urinary excretion.

In another study by Petreska Stanoeva & Stefova 2013, the authors investigated the urinary metabolites of flavonoids, phenylethanoid glycosides and hydroxycinnamic acids when *Sideritis scardica* decoction was given to humans. In the *Sideritis* decoction 31 phenolic compounds were identified and the total content was found to be 1450 ± 8 mg in 8 g of dried aerial part of *S. scardica* used for the preparation of the decoction. The study with ten volunteers was performed in two phases. First, the volunteers followed a polyphenol-restricted diet and received the *Sideritis scardica* decoction with following daily urine collection. In the second phase, the polyphenol-restricted diet was released but drank the *Sideritis* decoction with following daily urine collection (also 24 h after ingestion). The metabolites were characterized as hypolaetin, methylhypolaetin, isoscutellarein, methylisoscutel larein, and apigenin and 32 phenolic acid metabolites. The authors reported about the urinary excretion of polyphenol metabolites which corresponded to 5% (n/a) of the intake of polyphenols by the decoction. The most abundant flavonoid metabolites in urine samples were analyzed to be of 87-94% of the total polyphenolic metabolites content. Mostly methylhypolatein and methylisoscutellarein glucuronides have been found as metabolites. The urinary excretion of isoscutellarein was evaluated as 10 times higher than that of hypolaetin and apigenin showed high urinary excretion.

### 3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

No toxicology studies have been retrieved from the literature. However, some in-house data are available which have been performed on behalf of a private company (Finzelberg GmbH & Co. KG.).

Toxicity and genotoxicity studies performed on behalf of a private company.

No toxicology studies have been retrieved from the literature. However, some in-house data are available which have been performed on behalf of a private company xicity and genotoxicity studies performed on behalf of a private company.

#### 3.3.1. Single dose toxicity

**Acute toxicity**

A *Sideritis* herb extract, sicc., (70% native, 30% maltodextrin; extraction solvent: 20% v/v ethanol), has been tested in an acute oral toxicity study in Sprague Dawley rats ([IN HOUSE DATA 2011a](#)). The study has been performed according to the OECD guideline for the Testing of Chemicals. No gross or histopathological abnormalities and no signs of toxicity or mortality could be detected in all six female rats throughout the study period of 14 days when treated at the dose level of 2000mg/kg of the test item. The tested *Sideritis* herb extract has been assigned to category 5 covering the range for oral LD50 to be 2000mg/kg-5000mg/kg bw.

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1 (No. 423, Section 4: Health Effects) "Acute Oral Toxicity- Acute Toxic Class Method "Adopted on 17th December 2001."
3.3.2. Repeat dose toxicity

A *Sideritis scardica* herb extract, sicc., (70% native, 30% maltodextrin; extraction solvent: 20% v/v ethanol), has been tested in a repeated dose 28 day oral toxicity study in Sprague Dawley rats followed by a 14 day recovery period (IN HOUSE DATA 2011b). The study has been performed according to the OECD guideline for testing chemicals No. 407, "Repeated dose 28 day oral toxicity study in rodents" adopted on 3rd October 2008. The aim of the study was the investigation of the toxicological properties of the *Sideritis* herb extract on the target organ toxicity, and the "No Observed Adverse Effect Level (NOAEL) in rats (30 males and 30 females distributed to 6 groups with 5 rats/sex/group) after repeated oral administration during the study period of 28 days. The assayed extract, having been suspended in distilled water, was administered by gavage to animals at dosages of 250 mg/kg, 500 mg/kg and 1000mg/kg body weight and compared to the control groups having received distilled water only. Additionally, doses of 0 mg/kg and 1000 mg/kg were used to investigate the reversibility of possible delayed occurrence of symptoms.

All rats survived the study period, the body weight did not change, the food intake was comparable in all groups, and that no signs of toxicity could be found during the period of 28 days and the recovery period of 14 days. Furthermore, towards the end of exposure period the sensory reactivity of auditory, visual and proprioceptive stimuli did not show abnormalities in the treatment and control group. Hematological analysis revealed also no abnormalities except for an increase of the MCV and MHCH values at the dose of 1000mg/kg in male and in case of platelets at 1000mg/kg in female rat. A statistically significant decrease was documented for the values of total WBC at the dose of 500 mg/kg, male and MCHC (500 mg/kg, female) in male and female rats treated with different doses of the test item; however, the changes have been concluded to be marginal. No hematological changes have been caused by the *Sideritis* extract, except of a decrease of MCH in female animals from 1000 mg/kg reversal group sacrificed on day 43 but estimated to be in the biological range. Concerning the clinical biochemical parameters of Calcium and sodium (250mg/kg, 500mg/kg and 1000mg/kg, male), Chloride (250mg/kg and 1000mg/kg, female) and Sodium (500mg/kg and 100mg/kg, female) have been marginally influenced by the test item. The organ weight of the tested rats from different dose and control groups as well as from that of the reversal group (1000mg/kg) did not differ. Moreover, the pathological and histopathological examinations did not indicate any abnormalities which could be referred to the treatment with the *Sideritis scardica* dry extract.

In conclusion, the authors determined the NOAEL of the Sideritis scardica dry extract to be 1000mg/kg body weight in male and female animals when the Sprague Dawley rats were treated over a time period of 28 days in this repeated dose oral toxicity study.

3.3.3. Genotoxicity

According to the "Guideline on Selection of Test Materials for Genotoxicity Testing for Traditional Herbal Medicinal Products/Herbal Medicinal Products" (HMPC 2009) the genotoxicity test for the *Sideritis scardica* dry extract has been carried out in line with bracketing/matrixing-model. Four Ames tests with the dry extracts from *Sideritis scardica* herb of different polarity [water; 20 % (V/V) ethanol; 50 % (V/V) ethanol; n-heptane] have been evaluated for their genotoxic potential [. These extracts cover the entire spectrum of phytochemical constituents of the *Sideritis scardica* herb, including polar and non-polar constituents.

Four Ames tests with different polarity:

The dry extract of *Sideritis* (70% native, 30% maltodextrin; DER native: 4 – 8:1; extraction solvent water) was examined in the 5 *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA
1537 according to the plate incorporation test, each carried out without and with metabolic activation (AMES-TEST 2011). The first experiment was carried out as a plate incorporation test and the second as a preincubation test. In the experiment I the following concentrations of 31.6, 100, 316, 1000, 2500 and 5000µg/plate and in the experiment II 250, 500, 1000, 2000, 3000, 4000 and 5000µg/plate (only for TA 98 without metabolic activation) have been tested. For clarification of the results of tester strain TA100 in experiment I and II a third incorporation test was performed (only for TA 98 without metabolic activation) with the concentrations of 500, 1000, 2000, 3000, 4000 and 5000µg/plate. As a result, in all tester strains of I and II precipitation was found and additionally in experiment III at a dose of 5000µg/plate. No toxic effects have been observed under the test conditions. No increase in revertant colony numbers of any of the five tester strains have been observed in the presence or absence of metabolic activations in all experiments. In summary, the Sideritis extract e herb aquos. sicc. did not cause gene mutations by base pair changes or frameshifts in the genome of the tester strains used and therefore, the test item has been considered not to be mutagenic.

The dry extract of Sideritis (70% native, 30% maltodextrin; extraction solvent 20 % (V/V) ethanol) has been tested in the Salmonella typhimurium strains TA 97a, TA 98, TA 100, TA 1535 and TA 102 with and without metabolic activation (Dighe 2011). No cytotoxicity was observed when concentrations of 1µg/plate up to 5000µg/plate were used. Due to the results obtained by the cytotoxicity test following doses of the dry extract such as 61.72, 185.18, 555.55, 1666.67 and 5000µg/plate were chosen for the main experiment. No precipitation has been detected in any tester strains used and the number of revertant colonies was comparable to the control when metabolic activation was used or not.

The dry extract of Sideritis (70% native, 15% maltodextrin,15% silica; DER native: 6:1; extraction solvent 50 % (V/V) ethanol) has been tested in the Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537 and TA 102 with and without metabolic activation (AMES-TEST 2014a). The plate incorporation test (experiment I) and the pre-incubation test (experiment II) were performed with and without metabolic activation. In the experiment I the concentrations of 31.6, 100, 316, 1000, 2500 and 5000 µg/plate and in experiment II such as 10.0, 31.6, 100, 316, 1000, 2500 and 5000 µg/plate have been used. No precipitation was observed in any tester strain but toxic effects of the test item were seen in several tester strains in experiment I (at 1000 µg/plate and higher, without metabolic activation), and in experiment II (at 1000 µg/plate and higher, without metabolic activation) and at a concentration of 5000 µg/plate with metabolic activation.

As a result, biologically relevant increases in revertant colony numbers of any of the five tester strains have been noted under the treatment of the tested dry extract. In summary, the Extr. Sideritis e herb 50% ethanol sicc. did not cause gene mutations by base pair changes or frameshifts in the genome of the tester strains used and therefore, the test item has been considered not to be mutagenic.

The dry extract of Sideritis (50% native, 50% silica; DER native: 83:1; extraction solvent heptane) has been tested in the Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537 and TA 102 with and without metabolic activation (AMES-TEST 2014b). The plate incorporation test (experiment I) and the pre-incubation test (experiment II) were performed with and without metabolic activation. In the experiment I the concentrations of 3.16, 10.0, 31.6, 100, 2500 and 5000 µg/plate and in experiment II such as 1.0, 3.16, 10.0, 31.6, 100, 316, 1000, 2500 and 5000 µg/plate have been used. Precipitation was observed in all tester strains used in experiment I and II (with and without metabolic activation). Toxic effects were observed in four tester strains in experiment I at 31.6 µg/plate and higher without metabolic activation and in experiment II at 31.6 µg/plate and higher without metabolic activation as well as at concentrations of 1000 µg/plate and higher with metabolic activation.
3.3.4. Carcinogenicity

No carcinogenicity studies carried out on mountain tea herb in the scientific literature.

3.3.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies carried out on mountain tea herb was found in the scientific literature.

The safety of mountain tea herb during pregnancy and lactation has not been established. In accordance with general medical practice, the herbal medicinal products (herbal teas and other finished products) should not be used during pregnancy and lactation without medical advice.

3.3.6. Local tolerance

No data

3.3.7. Other special studies

No data available

3.3.8. Conclusions

No toxicology studies have been retrieved from the literature. However, some in-house data are available which have been performed on behalf of a private company. The toxicological data such as a single dose and a repeated dose study were summarized and presented. In the acute oral toxicity study a Sideritis herb extract, sicc. (70% native, 30% maltodextrin; extraction solvent: 20% v/v ethanol) no histopathological abnormalities and no signs of toxicity or mortality could be detected in rats when treated at the dose level of 2000mg/kg. The tested Sideritis herb extract has been assigned to category 5 covering the range for oral LD50 to be 2000mg/kg-5000mg/kg bw. The same extract has been tested in a repeated dose 28 day oral toxicity study in rats followed by a 14 day recovery period. No mortality and no changes in body/organs weight or food consumption have been observed and the NOAEL of the Sideritis scardica dry extract has been determined to be 1000mg/kg body weight.

According to the “Guideline on Selection of Test Materials for Genotoxicity Testing for Traditional Herbal Medicinal Products/Herbal Medicinal Products” (HMPC 2009) the genotoxicity test was conducted in line with bracketing/matrixing-model. Four Ames tests with dry extracts from Sideritis scardica herb of different polarity [water; 20 % (v/v) ethanol; 50 % (v/v) ethanol; n-heptane] have been conducted and thus, the entire spectrum of polar and non polar constituents of Sideritis scardica herb was considered. The four Ames-tests were negative in all test concentrations. The Ames tests were conducted according to GLP and in line with ICH guidelines (CPMP 1996; 1998). The tests were suitable to evaluate the genotoxicity of Sideritis scardica Griseb herb extracts and the results were unequivocally negative. The tests were performed in a bracketing/matrixing model according to the “Guideline on Selection of Test Materials for Genotoxicity Testing for Traditional Herbal Medicinal Products/Herbal Medicinal Products” (EMEA/HMPC/67644/2009) by conducting bacterial reverse mutation assays [Ames-test; OECD Test-No. 471 (OECD 1994)]. For the analysis of the mutagenic potential four Sideritis scardica dry extracts of different polarity (water, 20% and 50% v/v ethanol, and n-heptane) were tested covering the entire spectrum of phytochemical constituents including polar and non-polar constituents. In none of the four Ames tests a clear and dose related increase in the
number of revertants occurred and/or no biologically relevant positive response for at least one of the
dose groups occurs in at least one tester strain with or without metabolic activation; therefore Sideritis
scardica is not considered to be mutagenic.

The available toxicological data and the results of the Ames tests performed according to the
bracketing/matrixing-model support the positive safety profile of Sideritis scardica.

3.4. Overall conclusions on non-clinical data

Sideritis scardica Griseb.; Sideritis clandestina (Bory & Chaub) Hayek, S. raeseri Boiss & Heldr.,
Sideritis syriaca L., are botanically very closely related species of the same genus and have been
described as endemic species of the Balkan Peninsula growing wild and also cultivated since the last
century in Central Balkan and has been traditionally used as a healing aromatic herbal tea in folk
medicine of the Balkan countries since centuries. “Mountain tea” species (“Pirin tea” or “Mursalski tea”)
are widely used mainly for the relief of symptoms of lung diseases like cough of different origin and
gastrointestinal disorder. Furthermore, it is reported that the consumption of herbal teas from Sideritis
scardica Griseb.; Sideritis clandestina (Bory & Chaub) Hayek, S. raeseri Boiss & Heldr., and Sideritis
syriaca L., are helpful based on traditional knowledge for the relief of cough associated with cold, also
used for relief of mild gastrointestinal disorders. Pharmacological properties of the plant found in
relevant scientific literature like the anti-inflammatory and antimicrobial activities make the traditional
use in relief of cough associated with cold plausible. Moreover, published data referring to the
indications and preparations are limited, but existing data on the above-mentioned pharmacological
activities support the plausibility for the traditional use, for relief of cough associated with cold, of
Sideritis herba. Moreover the traditionally known use of the plant against gastrointestinal disorders is
considered in the knowledge of the results from an in vitro test of a n-butanol extract investigated by
Tadic et al. 2012 the anti-inflammatory, gastroprotective activities as well as Spasmolytic activities
with positive final outcome . These data indicate that Sideritis species act potentially as a spasmolytic
on intestinal smooth muscle, could further support their uses in gastrointestinal disorders (Brankovic et
al. 2011)

By in vivo studies, several phenolics belonging to Sideritis species like flavones and hydroxycinnamic
acids have been studied with regards to their absorption and metabolism by the human
gastrointestinal tract and following occurrence at systemic level in plasma and excretion by urine
(Meyer et al., 2006; Lafay et al., 2008; Jia et al., 2009; all cited in Petreska et al. 2011a).

The available toxicological data and the results of the Ames tests performed according to the
bracketing/matrixing-model support the positive safety profile of Sideritis scardica.

Due to the existing tests on genotoxicity on Sideritis scardica Griseb., an European Union list entry on
Sideritis scardica can be established.

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal
substance(s)/preparation(s) including data on relevant constituents

No data available
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available

4.2. Clinical efficacy

4.2.1. Dose response studies

No data available

4.2.2. Clinical studies (case studies and clinical trials)

No data available

There is a lack of clinical research, assessing the effects of mountain tea herb and rigorous randomised controlled clinical trials are required.

4.3. Clinical studies in special populations (e.g. elderly and children)

None reported

4.4. Overall conclusions on clinical pharmacology and efficacy

No data available

There is a lack of clinical research, assessing the effects of mountain tea herb and rigorous randomised controlled clinical trials are required.

The conclusions should include an assessment of the plausibility of efficacy of the herbal preparation(s)/medicinal product on the basis of long-standing use and experience.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

No data available

5.2. Patient exposure

No data available

5.3. Adverse events, serious adverse events and deaths

No data available

5.4. Laboratory findings

No data available.
5.5. **Safety in special populations and situations**

5.5.1. **Use in children and adolescents**

No data on the oral use in children and adolescents are available, therefore mountain tea can be intended only for adults and elderly.

5.5.2. **Contraindications**

Hypersensitivity to the active substance or to other plants of the Lamiaceae (Labiatae) family

5.5.3. **Special Warnings and precautions for use**

The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

5.5.4. **Drug interactions and other forms of interaction**

None reported

5.5.5. **Fertility, pregnancy and lactation**

No fertility data available.

In the absence of data available and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing mountain tea herb during pregnancy and lactation.

5.5.6. **Overdose**

No cases of overdose have been recovered in the scientific literature.

5.5.7. **Effects on ability to drive or operate machinery or impairment of mental ability**

No data in the literature search.

5.5.8. **Safety in other special situations**

No data in the literature search.

5.6. **Overall conclusions on clinical safety**

In the absence of adequate data on the use in children and adolescents, the oral use of mountain tea herb is intended only for adults and elderly.

In the absence of data available and in accordance with general medical practice, it is recommended not to use traditional herbal medicinal products containing mountain tea herb during pregnancy and lactation.

No fertility data available.
Moreover no adverse effects have been reported, showing enough safety data for the proposed traditional use of herbal medicinal products containing mountain tea, in the conditions for a safe use found in the monograph.

6. Overall conclusions (benefit-risk assessment)

The present assessment of Sideritis scardica Griseb., Sideritis clandestina, S. raeseri and S. syriaca was established on the basis of a recently performed literature research. Sideritis scardica Griseb, S. raeseri, S. syriaca and Sideritis clandestina have been described as very closely related botanically endemic species of the Balkan Peninsula and have been traditionally used as healing aromatic herbal teas in folk medicine of the Balkan countries. "Mountain teas" ("Pirin tea" or "Mursalski tea") often used for domestic use and consumption have been described mainly for the relief of cough of different origin but mainly associated with cold. Furthermore, it is reported that Sideritis scardica Griseb, S. raeseri; and Sideritis clandestina are traditionally used for the treatment of inflammation, gastrointestinal disorders, and cough associated cold Pharmacological properties of the plants found in relevant scientific literature like the anti-inflammatory, gastro protective and antimicrobial activities could support to these indications.

The positive effects of mountain tea herb on the relief of symptoms of cough associated with common cold have been recognised empirically. There is also a long-standing traditional use in part of Europe of the plant for the relief of gastrointestinal disorders. Furthermore, gastro-protective and spasmyloytic effects have recently been evaluated. On the basis of the long-standing use and the experiences in the folk medicine the use of Sideritis scardica Griseb., Sideritis scardica and Sideritis clandestina and S. syriaca are regarded not to be harmful in the uncomplicated specified disorders mentioned above.

The uses are made plausible by the long-standing use and experience, having regard also to existing in vitro pharmacological data.

There is a lack of controlled clinical studies with preparations containing Sideritis sp. (Sideritis scardica Griseb.; Sideritis clandestina(Bory & Chaub) Hayek, S. raeseri Boiss & Heldr., Sideritis syriaca L.)

In conclusion, mountain tea (Sideritis scardica Griseb.; Sideritis clandestina(Bory & Chaub) Hayek, S. raeseri Boiss & Heldr., Sideritis syriaca L.) and their preparations can be regarded as traditional herbal medicinal products in the following indications:

1. Traditional herbal medicinal product used for the relief of cough associated with cold.
2. Traditional herbal medicinal product used for the relief of mild gastrointestinal disorders.

In the absence of adequate data in adolescents and children, the oral use of preparations containing Sideritis scardica Griseb.; Sideritis clandestina(Bory & Chaub) Hayek, S. raeseri Boiss & Heldr., Sideritis syriaca L. herba are intended only for adults and elderly.

In the absence of available data and in accordance with general medical practice, it is recommended not to use traditional herbal medicinal products containing mountain tea during pregnancy and lactation.

**Due to the existing data of genotoxicity tests, an European Union list entry could be established on Sideritis scardica Griseb.**

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.
Annex

List of references