HerbalDrugMonograph

Herba Sideritis: a promising adaptogen with thepotential to reduce the risk of age-related cognitivedeclineand neurodegenerativedisorders.

Abstract

Background. Traditional use of Greek mountain tea (GMT), Herba Sideritis (*Sideritisscardica*Griseb.), isused to treat the common cold and mild gastrointestinal disorders. Recent studies suggest its potentialefficacy for reducing the risk of age-related cognitive decline and neurodegenerative diseases, whichcouldbeassociatedwith thecommonmechanismsofaction.
*Aimsandhypothesis.*Theaimsofthismonographwere:(i)toelaborateararionaleforamodeofpharmacological action, which is likely associated with a regulation of the neuroendocrine-immune complex(stress system), and (ii) to systematically update new evidence of the quality, efficacy, and safety of GMTpreparationsand validate theirpotentialhealthbenefits.
*Methods.*LiteraturescreeningusingthePubmeddatabaseandoriginalpublicationswereassessedaccording to WHO criteria for monographs of herbal medicines. *Results. Sideritisscardica*extracts and itsingredient phenylethyl-phenylpropanoid glycoside acteoside (AC, *syn.* verbascoside) exhibited cognitiveimprovement, stress-protective, neuroprotective, neurogenesis, anxiolytic, ~~anti-aging~~anti-ageing, anti-inflammatory,antimicrobial, gastroprotective, glycemic, anti-obesity, antioxidant, and anti-tumor activity. The recentfindings supported by preclinical and clinical data suggest using Herba Sideritis extracts to improvecognitivefunctionsand mentaldisordersin~~aging~~ageing.
*Conclusion.*Thismonographprovidessystematicinformationonthesafety,efficacy,andqualityofHerbaSideritis, paving the way for its potential use in reducing the risk of age-related cognitive decline andneurodegenerative disorders. Further preclinical and clinical research is crucial to fully validate GMT'shealthbenefitsandunravelthe mechanismsunderlyingitsadaptogeniceffects.

*Keywords:*HerbaSideritis,*Sideritisscardica,*monograph,cognitivefunctions,herbalmedicine.

Introduction

Mount Olympus is the legendary home of the Greek gods. It's the mythological home of the most reveredsymbols of the ancient Greek religion and a physical symbol; it's one of Europe's highest peaks, soaringmore than 9,500 feet above the serene Aegean Sea. The sacred mountain is high, dry chaparral with awealth of biodiversity, the birthplace of one of the Greek Mountain Tea (Sideritisscardica: translation "hewho is made of iron"), frequently called "Olympos" tea by Greeks and their Mediterranean
~~neighbors~~neighbours.Alsocalled"ironwort"or"shepherd'stea,"GreekMountainTea(GMT)growswildataltitudesabove

3,200 feet. It's a survivor, growing wild and thriving on poor soil and a limited amounts of water. MostGreek Mountain Tea is wild-grown, harvested by local farmers, and minimally processed at those samehighaltitudes.Itspopularityiswell-deserved.Inancienttimes,Greekshepherdsbegantoharvest GMTto help them stay healthy, warm, and mentally alert.The medicinal use of Greek mountain tea (GMT)was described by theGreek physicianDioscorides in De Materia Medica in 77 C.E. Hippocrates, thefather of modern medicine, lauded GMT's benefits for immune dysfunction and respiratory illnesses.Greeks still use the tea today to combat winter colds and flu. They also used GMT for wound healing,especially wounds caused by iron weapons, hence the nickname "ironwort." In modern times, GMT hasbeen widely acclaimed for its vast healing power. Modern scientific research confirms GMT can combatAlzheimer's disease, lower blood pressure, reduce the risk of heart attacks and strokes, improve digestivehealth, increase bone density, enhance immune function and prevent colds and flu, reduce anxiety anddepression, reduce insulin resistance, promote weight loss, relieve joint pain. The most exciting for us isGMT'seffectivenessagainstAlzheimer'sdiseaseanddementia,confirmedthroughseveralwell-researched published studies. All these benefits sound like a recipe for a healthy, long life, especially forolderadults.Thisisthesubjectofthisbookchapter,sothesefindingswillbeaddressedindetail(Lemerond, 2023).

GMT was adopted in 2015 in the European Union as traditional herbal medicine, Herba Sideritis (*Sideritisscardica*Griseb.), for treating the common cold and mild gastrointestinal disorders; however no registeredorauthorizedwell-establishedmedicinalproductsintheEU/EEAMemberStates(EMA/HMPC/39455/2015). Since then, considerable studies have been conducted suggesting that GMTcan reduce the risk of age-related cognitive decline and neurodegenerative disorders (Dimpfel, 2013;Dimpfel et al., 2016a; Dimpfel et al., 2016b ;Behrendt et al., 2016;Hofrichter et al., 2016; Heiner et al.,2018; Feistel et al.2018; Chalatsa et al., 2018; Wightman et al., 2018; Jeremic et al.,2019; Żyżelewicz et al.,2020; Sklirou et al., 2021; Vasileva et al., 2022; Lazarova et al., 2023; Yanchev et al., 2023; Ververis et al.,2023;Tumouetal., 2023).

The recent findings supported by preclinical and clinical data suggest using Herba Sideritis extracts toimprovecognitivefunctionsandmentaldisordersinaging.Furthermore,recentpublicationsshow*Sideritissca rdica*extractsandsomepurifiedcompoundsexhibitedcognitiveimprovement,stress-protective,neuroprotective,anxiolytic,~~anti-aging~~anti-ageing,anti-inflammatory,antimicrobial,gastroprotective,glycemic,anti-obesity,antioxidant,andanti-tumoractivity.SuchpleiotropiceffectsofGMTontheneuroendocrine-immune complex (stress system) are typical of adaptogenic activity (Wagner et al.1993:Panossian&Efferth,2022;Panossianetal2021; Panossianand Brendler, 2020;Panossian, 2017;).

This monograph provides scientific information on the safety, efficacy, and Quality of the widely usedmedicinal plant *Sideritisscardica*Griseb and provides a rationale for the adaptogenic activity of GMP(Panossian, 2023).

Herbalname

*Sideritisscardica*Griseb. (order Lamiales, family Lamiaceae, genus *Sideritis*) is an Internationally acceptedname (WFO PlantList, 2023) for Herba Sideritis. The Latin name Sideritis L. derives from the Greek word"sideros" (iron), assuming that this herb healed wounds caused by iron-made weapons in ancient times(González-Burgos, et al., 2009, cited in Font Quer, 2000). Herba Sideritis consists of the whole or cut, driedfloweringtopsor aerialpartscollectedduringthe floweringseason.

Synonyms

- *Navicularia scardica* (Griseb.) Soják
- *Sideritis florida* Boiss. & Heldr.
- *Sideritis raeseri* subsp. Florida (Boiss. & Heldr.) Papan. & Kokkini
- *Sideritis scardica* subsp. *Longibracteata* Papan. & Kokkini

Selected vernacular names

Various vernacular names have been ascribed to the plant in the ancient world (Gonzales-Burgos et al., 2011; Govaerts, 2003 cited in Feistel, 2013 and EMA/HMPC/39454/2015; Kazaryan, 1981; Todorova & Trendafilova, 2014), including:

- Ελληνικό Τσάι του βουνού / Greek mountain tea, 'Olympus tea' (Greece),
- Caj Mali (Albania),
- Mursalski Tee, Pirinski Tee or 'Alibotushki tea' (Bulgaria),
- Планинскичај / Planinski Tea, 'Sharpla-ninsichaj' (FYROM),
- "Rabo de gato" or "zahare˜na" (Spain)
- Greek Mountain Shephard's (Tea England/UK),
- Griechischer Bergtee (Austria),
- Griechischer Bergtee / Greek Mountain tea, Griechisches Eisenkraut / Greek ironwort (Germany),
- Железница / Greek ironwort (Russia),
- Ե ր ն ջ ա / Ernja (Armenian).

Geographical distribution

Sideritis ssp. has been characterized as a genus with more than 150 perennial species widely distributed in the Mediterranean and the Canary and Madeira Islands (Bojovic et al., 2011). The plants grow in the Balkan peninsula, while 17 species are indigenous in Greece alone. *Sideritis scardica* Griseb. is native to the Balkans and the Iberian Peninsula but can also be found in Central Europe and West Asia (Kaparakou et al., 2023; Chrysargyris et al. 2023; Plants of the World Online, 2023; Bojovic et al., 2011; Petreska et al., 2015; Grdiša et al., 2019). The plant is growing on rocky slopes at elevations over 1000 m on the central part of the Balkan Peninsula, including Greece, FYROM (Former Yugoslavian Republic of Macedonia), Bulgaria, Serbia, Albania, and Turkey) (Kaparakou et al., 2023; Heywood, 1972; Petreska et al., 2015). The *Sideritis scardica* was included in the threat category "endangered" on the *Red list of Bulgarian vascular plants*, *Red Data Book of the Republic of Bulgaria,* and in the list of medicinal plants under special regime for conservation and use due to its intensive collection for years (Todorova et al., 2014).

Description

A hardy perennial herb, 40–80 cm in height with creeping roots; lower leaves 40-80 x 6-20 mm oblong-lanceolate; verticillasters crowded into a dense spike; middle bracts 12-20 mm, subarticular-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 (Heywood, 1972; Flora Europaea Vol. 4, 2009)

Plantmaterialofinterest:driedaerialparts

Generalappearance.

Hardyperennialwithcreepingroots.

- Stems - in the bottom are woody, 15-50 cm tall, flower-bearing stems (sprigs)-erect or prostrate, 4-angle; simple or branched(usuallyunbranched).
- Leaves - opposite, entire (smoothed) or serrated leaf blade, leaves vary by their shape: fromoblanceolate (long lanceolate) to obtuse - in the lowest veins; to longer in the middle veins; tolanceolate (linear-lanceolate) - acute in the highest veins. Lower leaves have a short stalk, 40-80mm long, 6-20 mm wide. Upper leaves from the 4th vein upward are prostrate as the stem isshortened graduallyfromlower toupper leaves.
- Bracts have an almost elliptical shape (wide heart shape at the base, acutely pointed to the apex)with soft skin consistency. When ripening, they get lemon-yellow ~~color~~colour. In the first vein, they are38mmlongand50-80mmwideastotheapexoftheinflorescence;theirdimensionsdecrease.
- Flowers are gathered in dense spike-like inflorescences, 50-80 mm long, about 30 mm wide; thereceptacleistubecup-shaped,withtenveinsandfive equalteeth,pubescentand coatedbyfineintertwined hairs. The whorl is yellow with a tube hidden in the receptacle, two-lipped with athree-lobelowerlip. Fourstemsare hiddeninthetubesofthe whorl.
- The fruit is dry and decomposed into four nuts. Leaves and stems are white, woolly-villous(Heywood,1972;Yaneva&Balabanski, 2013)

Depending on the sea level and climate properties, the plant comes out in blossom from the end of Juneto the beginning of September. (Heywood, 1972). GMT is one of the medicinal and aromatic ~~plant~~ plantswith ~~greatglobal~~ great global economic importance due to its nutritional value, pharmacological activities and potentialapplicationsinthe cosmeticand perfumeindustries(Kaparakouetal.,2023).

Organolepticproperties

Itssmellispleasant,andthetasteisslightlybitter(Heywood,1972).GMTinfusionshaveapleasantcharacteristicaroma(Chrysargyrisetal. 2023).

Microscopiccharacteristics

Nodataavailable

Powderedplantmaterial

Aerialpart:nodataavailable.

Generalidentitytests

Macroscopic examinations (Heywood, 1972), thin-layer chromatography (Heiner et al., 2018; Feistel et al.,2018;Pihanetal., 2021), and HPLC(Mrozetal., 2023;Heineretal., 2018;Feistel etal., 2018).

Puritytests

Microbiological

Tests for specific microorganisms and microbial contamination limits were described in the WHOguidelines on assessing the Quality of herbal medicines with reference to microbiological contaminants(QualityCcontrol Mmethodsfor MmedicinalPplantMmaterials, 1998).

Foreignorganicmatter

Aerial part: not more than 2% as described in the WHO guidelines on assessing the Quality of herbalmedicines with reference to foreign organic matter (Quality control methods for medicinal plantmaterials,1998).

Totalash

*Aerialpart:*notmorethan10%asdescribedintheWHOguidelines onassessingtheQualityofherbalmedicineswithreferencetototalash(Qualitycontrolmethodsfor medicinalplantmaterials,1998).

Acid-insolubleash

Aerial part: not more than 2.5% as described in the WHO guidelines on assessing the Quality of herbalmedicines with reference to acid-insoluble ash (Quality control methods for medicinal plant materials,1998).

Water-solubleextractive

Aerialpart:notlessthan15.0%asdescribedintheWHOguidelines onassessingtheQualityofherbalmedicines with reference to water-soluble extractives (Quality control methods for medicinal plantmaterials,1998).

Lossondrying

Aerialpart: notmore than 12%w/w(Hofrichteretal.,2016); 5.5%w/w/ (Mroz etal.,2023).

Pesticideresidues

The recommended maximum limits of pesticides (European pharmacopoeiaPharmacopoeia, 2008) and the WHOguidelines on assessing the Quality of herbal medicines with reference to contaminants and pesticideresidues(Qualitycontrolmethodsformedicinalplantmaterials,1998).

Heavymetals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on assessing the Qualityof herbal medicines with reference to contaminants and residues (Quality control methods for medicinalplantmaterials, 1998).

Radioactiveresidues

Where applicable, consult the WHO guidelines on assessing the Quality of herbal medicines withreferencetocontaminantsandresidues(Qualitycontrolmethodsformedicinalplantmaterials,1998).

Comment [PB1]: Use capital words for every word here where you use it. It is used multiple times.

Chemicalassays

***Total polyphenolics*:** not less than 5.82–15.0% (mean content 8.6 ± 2.6%) (Petreska et al., 2011); 5.4 ±0.2%(Grozdanova etal.,2020),10.1%± 0.1%(Lazarova etal.,2023),13.5%(Danesietal.2012). Alternatively,thetotalpolyphenolscontentwasdeterminedusingFolin-Ciocalteu'sreagentandgallic

acidasacalibrationstandard;theresultswereexpressedinmggallicacidequivalentsper100gdryweight(Lazarovaet al.,2023).

Majorprincipalcomponentsanalysis

- Acteoside/verbascoside**(5):** not less than 0.71–2.24% (mean content 1.8 ± 0.0.45%) (Petreska et al.,2011);0.12-1.54%- indriedwater- ethanolicextracts(Heineretal.,2018;Feisteletal.,2018).
- Lavandulifoliside**(8)** :notlessthan0.67–2.61%(meancontent 1.26±0.65%),
- Iso-scutellarein 7-O-[6'''-O-acetyl]-allosyl(1→2)-glucoside,**(1):**not less than 0.3–1.1% (meancontent0.6±0.25%),
- 4'-O-Methylhypolaetin 7-O-[6''' -O-acetyl]-allosyl(1→2)-glucoside **(3):** not less than 0.56–1.23%(meancontent0.84±0.21%)(Petreskaet al.,2011).

***Totalphenylpropanoids*:**notlessthan2.88–9.68%(meancontent5.1± 1.95%)(Petreska etal.,2011a)analysed by liquid chromatography -diode array detector – electrospray using high-performance liquidchromatography coupled to UV-Vis diode array detection and tandem mass spectrometry with anelectrospray ionization source (LC/DAD/ESI-MS) (Petreska et al., 2011a) and high-resolution massspectrometryHR-LC-ESI-Orbitrap-MS/MSanalysisinnegativeionmode(Mroz etal.,2023).

Hydroxycinnamic derivatives: not less than 0.08–0.58% (mean content 0.22 ± 0.15%) (Petreska et al.,2011).Hydroxycinnamicacidswerequantifiedusing5-caffeoylquinicacidasexternalstandardat330nm;identification of hydroxycinnamic acid derivatives containing caffeic, ferulic, and coumaric acid moietieswas conductedbyUV detectionof twopeaksdetectedbyabsorptionbandsat 320-325nmand 242nmand by a sharp diagnostic shoulder at 290-300 nm that typical of compounds containing ahydroxycinnamicgroup (Petreskaet al., 2011).

Phenylethanoid glycosides: not less than 2.8–9.1% (mean content 4.8 ± 1.8%) (Petreska et al., 2011);phenylethanoid glycosides containing 5-caffeoylquinic acid moiety were quantified and expressed asverbascoside equivalents at 330 nm; Identification of phenylethanoid containing phenylpropanoids wasby absorption peaks at 232, 246, 288 and 332 nm and fragmentation patterns characteristic ofphenylethanoid glycosides acylated with caffeic acid and ferulic acid, thus allowing their identification asglycosylhydroxycinnamicacids(Petreskaetal., 2011).

Total flavonoids: not less than 2.55–5.65% (mean content 3.3 ± 0.8%)(Petreska et al., 2011)*;* 1.14 ±0.02% (Grozdanova et al., 2020). Hypolaetin, luteolin, and chryseriol glucosides were quantified with 4'-O-methylhypolaetin 7-O-[6‴-O-acetyl]-allosyl(1→2) glucoside at 290 nm; apigenin and isoscutellareinglucosides were quantified and expressed as isoscutellarein 7-O-[6‴-O-acetyl]-allosyl (1→2)glucosideequivalentsat300nm.Alternatively,thetotalflavonoidcontentwasdetermined usingAlCl3reagentandexpressed asmgquercetinequivalentsper 100gdry weight(Lazarovaet al.,2023).

***Totalflavones*:**notlessthan0.20- 0.50± 0.02%(Janeskaetal.,2007).

Flavonoid-7-O-diglycosides: notlessthan0.05–0.52%(meancontent 0.24±0.15%)(Petreskaetal.,2011).

Flavonoidacetylglycosides:notlessthan2.5–5.13%(meancontent 3.3± 0.8%)(Petreskaetal.,2011).

Diterpenes*(Siderolandsideridiol):*0.13-1.8%(Ibraliuetal.,2014).

Essential oil: not less than 0.03% (% volume per weight of herb, v/w) of etheric oil determined bysteam distillation (Bojovic et al., 2011); the content of etheric oil very from not detectable to 0.45%depending on the geographical location of the herb (Kaparakou et al., 2023; Chrysargyris et al.2023). GC-MS and GC-FID qualitative and quantitative analysis show the presence of 64 volatile compounds(Hajdari et al., 2020)where the main monoterpenes were β-pinene (17.9%), α-pinene (7.3%), carvacrol(14.8%),menthol(8.5%)andgeraniol(5.6%)(Bojovic etal., 2011;Tadić, Bojović, et al., 2012a;Kaparakouet al., 2023).

Majorchemicalconstituents

Over 200 plants' secondary metabolites have been identified in the aerial part of *Sideritisscardica*,comprising a complex of polyphenolic compounds,monoterpenes, sesquiterpenes, diterpenoids,triterpenes, and aliphatic compounds (Kostadinova et al., 2007; Petreska, Stefkov, et al., 2011a; Petreska,Stefova, 2011b; Bojovic et al., 2011; Tadić, Bojović, et al., 2012a; Fraga, 2012;Karapandzova et al., 2013;Yaneva & Balabanski, 2013; Papaefstathiou et al., 2014; Todorova et al., 2014;Qazimi, et al., 2014;Ibraliuet al., 2015; Stanoeva et al., 2015; Zyzelewicz et al., 2020; Hajdari et al., 2020; Dina et al., 2022;Pihan, et al.,2021; Mroz et al., 2023; Ververis et al. 2023; Chrysargyris et al.2023; Kaparakou et al., 2023; Tomou et al.,2023; Yanchev et al., 2023;). In one study (Danesi et al.,2013) the content of caffeine was declared less <than 80 g kg−1 in Herba Sideritis water extract according to the manufacturer (Indena, Italy), however itwas identified in that study(Denessi et al.,2013) and other phytochemical studies of siderite extracts,whichisknowfree ofcaffeine (Zyzelewicz et al.,2020;Walbroel,and Feiste,2010).

Comment [PB2]: What does this mean? I could not understand the language.

*Sideritisscardia*is a rich source of polyphenols with a content range from 5.8% to 15.0% of dry plantmaterial. The largest portion of polyphenols consists of **phenylpropanoids** (caffeoyl-, feruloyl-, andcoumaroyl-esters) derivatives (2.88–9.68%), containing phenylethanoid-glycosides moiety (2.8–9.1%,includingAcetoside,Allysonoside,Echinacoside,ForsythosideA,Lavandulifolioside,Leucoseptoside A,Martynoside, Verbascoside, Isoverbascoside, Samioside), *monoterpenoids (*iridoids*)(*Stachysosides E **(10),**StachysosidesG, Melittoside , Chlorogenic acid), and other phenolic acids (3-caffeoyl-, 5-caffeoyl-,feruloyl-quinic acids, syringic, vanillic, protocatechuic, p-coumaric and ferulic acids, 0.08–0.58%)(Petreska et al., 2011). The second large part of aromatic compounds is **8-OH flavone 7-O-glycosides**,containinghypocretinand iso-scutellareinaromaticcoresintheirstructure(2.55–5.65%).

Among 102 compounds identified in 70% ethanolic extracts of *Sideritisscardica*areal parts (Mroz et al.,2023),themainmajor activeconstituentsincluded:

- ***flavone 7-0-glycosides*** Iso-scutellarein 7-O-[6'''-O-acetyl]-allosyl(1→2)-glucoside **(1),** Iso-scutellarein7-O-[6'''-O-acetyl]-allosyl(1→2)-[6''-O-acetyl]-glucoside **(2),** 4'-O-Methylhypolaetin 7-O-[6''' -O-acetyl]-allosyl(1→2)-glucoside **(3),** 4'-O-Methylhypolaetin 7-O-[6'''-O-acetyl]-allosyl-(1→2)[6'''-O-acetyl]-glucoside**(4);**
- ***phenylethyl-phenylpropanoids glycosides*** acteoside/verbascoside**(5),** Iso-acteoside**(6),** ForsythosideB **(7)**,Lavandulifolioside**(8)**,Samioside**(9)**and ***phenylpropanois*****(10)**
- ***monoterpenoid (*iridoids*) phenylpropanoids glycosides*** Stachysosides E **(11),** StachysosidesG **(12)**,Melittoside (**13**),Chlorogenic acid**(14),**andD-(−)-Quinicacid**(15);**
- ***Diterpenes***Siderol(**16)**andsideridol(**17**).

Chemicalstructures1-17here.

The content of acteoside (*syn.* verbascoside) was highest in 20% EtOH (v/v) S. scardica extract containing6.25% total polyphenols including flavonoids (1.18%) and caffeoylquinic acids (0.41%) compared with S.scardicaextractsusedwater,50%ethanolandheptane asextractionsolvents(Heineretal.,2018;Feisteletal.,2018), Figure 1.

Figure1here.

Another representative HPLC fingerprint of *Sideritisscardica*70% ethanolic extracts is shown in Figure 2(Mroz et al., 2023). Differential analysis of *Sideritisscardica*and *Sideritisraeseri*extracts proved thatsubstance peaks were assigned in favor of the *S. scardica*variety; among peaks assigned in favor of the *S.scardica*, 10 main compounds were selected for distinction between these varieties including twoprominent peaks of Iso-scutellarin 7-O-[6'''-O-acetyl]-allosyl(1→2)-[6''-O-acetyl]-glucoside **(2),** 4'-O-Methylhypolaetin 7-O-[6''' -O-acetyl]-allosyl(1→2)-glucoside (3), 4'-O-Methylhypolaetin 7-O-[6'''-O-acetyl]-allosyl-(1→2)[6''' -O-acetyl]-glucoside **(4);** in contrast, the 4'-O-Methyl-*iso*-scutellarein-7-O-[6'''-O-acetyl]-allosyl(1→2)-glucoside'swasthemajor in*S. raeseri*extract (Mroz et al.,2023).

Figure2here.

Acteoside is presumably the most suitable quality control active marker, **Figure** 1, for drug development(Heineretal.,2018;Feisteletal.,2018)inclinicalstudies(Wightmanetal.,2018; Dimpfeletal.,2016b),duetoitsknown neuroprotective,anti-inflammatory,antibacterialandantileishmanialactivity(Moussaviet al., 2022). Acteoside, was pharmacologically active *in vitro* and *in vivo* models of neurodegenerative,behavioral,andotherstressandstress-inducesdisorders(Alipievaetal.,2014;Khanetal.,2022;Xiaoetal.,2022;Zhao etal.2023),suggestingthat they can beusedas activemarkersofquality ofstandardizedor quantitative extracts of Active Pharmaceutical Ingredient to ensure of reproducible efficacy of GMTmedicalproducts(Heineretal.,2018; Feistel et al., 2018).

However, further studies are needed to demonstrate the additive, potentiating, or synergistic effects andlack of antagonistic interaction of other GMT ingredients, including their dose-response andpharmacokinetic studies in matching doses to GMT. Thus, synergistic effects between acteoside,chlorogenicacidandflavonoids,mightplausiblyplayaroleinthehealthbeneficialandnootropicprofileofS. scardicaparticularlyinAlzheimer Disease(Moussavietal.,2022).

The chemical structure of Acteoside/Verbascoside includes dihydroxyphenyl-propenyl (C6–C3) anddihydroxyphenyl-ethyl (C6–C2) pharmacophores covalently attached to sugar moieties. It is widelyspread in the plant kingdom; it occurs in numerous species in all the families of Lamiales and manyfamilies of Asterales, Cucurbitales, and Mangoliales orders (Alipieva et al., 2014). They have differentchemicalcompositions,pharmacologicalsignatures,andprofilescomparedtoGMP,whichdiffersfromany purified active constituent. In this context, an assertion that acteoside is the only compound"responsible"for the activityof GMTislikelyunjustified.

Twenty minerals in over-ground parts of the plant and in water tea-infusions were determined. As mostaffluent, the following minerals were K > Ca> Mg> P> Fe > Al > Na, and microelements, as well asdesignatedtoxicelements,weregiven inthefollowingorder: Zn>Mn >B >Ba >Cu >Sr>Li>Ni> Cr>Co, and Cd> Pb > As, respectively. In the case of water tea infusions, a large portion of K, P, Na, Cu, andPb,butsmalleramountsoftheotherelementshavebeenfound(Bojovicetal.,2011;Yaneva&Balabanski,2013).

Medicinaluses

Usessupportedbyclinicaldata.
Mental enhancement and improvements in cognitive performance (Behrendt et al., 2016; Dimpfel, 2016a;Dimpfel,2016b;Wightmanet al., 2018***)***

Usesdescribedinpharmacopeiasand well-establisheddocuments.
An ancient Pharmacopoeia of medicinal plants and medicines dated 1stBC describes the use of HerbaSideritis wet packs or compresses in wound healing(Dioscorides s, De Materia Medica IV, 37). There isno existing monograph in National Pharmacopoeias or National Codexes currently used in the MemberStates or any other monograph on Sideritis herba. There are no registered or authorized well-establishedmedicinalproductsinthe EU / EEAMember States(EMA/HMPC/39455/2015).

Usesdescribedintraditionalmedicine.
Greek mountain tea was traditionally used as anti-inflammatory, anti-ulcerative, antimicrobial, antiseptic,vulnerary, antispasmodic, anticonvulsant, analgesic, and carminative preparation in common colds,rhinitis, sore throat, angina pectoris, bronchitis, bronchial asthma, lung emphysema, rheumatic disorders,anemia, chronic kidney disease, prostatic hyperplasia, herpes, wound healings, herpes, and clearing thebodyofpoisons (Gonzales-Burgosetal.,2011; Todorova et al.,2014; Tsioutsiou etal.,2019). According to EMA Assessment Report on SideritisscardicaGriseb., 2016, mountain tea has beentraditionally used to aid digestion, strengthen the immune system, and suppress the common cold, theflu. The evidence of traditional medicinal use of Sideritis herba is confirmed by a large number ofpublications providing consistent information (EMA/HMPC/39454/2015). The indications of SideritisHerba for the relief of cough associated with cold and mild gastrointestinal disorders were adopted forthe European Union monograph (EMA/HMPC/39455/2015; EMA/HMPC/80270/2016;EMA/HMPC/M/H/183). The monograph describes the comminuted herbal substance as herbal tea(infusion,decoction) for oraluse(EMA/HMPC/39453/2015).

Pharmacology

Experimentalpharmacology –preclinicalinvitroandvivostudies

Primarypharmacodynamics

Primarily pharmacodynamics studies of *Sideritisscardica*water extract are related to adopted traditionaluse in common cold and mild gastrointestinal disorders, supported by results of antibacterial and anti-inflammatory effects of *Sideritisscardica*water extract in experiments *in vitro* and *vivo.* Meanwhile, recentpreclinical and clinical studies of *Sideritisscardica*alcoholic extracts suggest their potential use in thetreatment of cognitive and mental disorders, which can be included in the main indication for evidence oftheuse ofthenewmedicinalproduct.

Cognitivefunctions,mentaldisorders,andneuroprotectiveactivity

*Sideritisscardica*extracts reduced behavioral anxiety, depression, and memory loss in animal models,improving their memory and learning (Dimpfel, 2013; Hofrichter et al., 2016; Lazarova et al., 2023). Inaddition, *Sideritisscardica*extracts reduced amyloid-β aggregation and neurotoxicity in AlzheimerDisease mouse models, in nematode *Caenorhabditis elegans*, and neuronal cell lines [Hofrichter et al.,2016;Heiner et al., 2018; Chalatsaet al., 2018].

A hypotheticalmechanisms of action of GMT against in stress-induced and aging-related disorders,includingmildcognitivedisorders,Alzheimerdisease,mood,anxiety,depressionanddepressive-likebehavior, aremainlybased ondysregulationsof:

- neurotransmitter systems, including monoamines (dopamine, norepinephrine and serotonin)(KnörleandSchnierleP. 2005;Knörle,2012;FeistelandWalbroel,2012;Lazarovaetal.,2023);andactivation ofdopaminergic,norepinephrinergic,serotonergicand thecholinergicneurotransmission (Dimpfel,2013;Dimpfelet al.,2016a;Dimpfeletal., 2016b);
- neurodegeneration and triggering of amyloid- β (A β) deposition (Hofrichter et al.,2016; Heiner etal.,2018; Chalatsaetal.,2018;Ververiset al., 2023);
- impairedneurogenesis(Tumouetal.,2023);
- chronic oxidative stress, neuroinflammation, and inflammageing (Danesi et all, 2013; Jeremic etal.,2019; Tadićetal.,2007;Tadićetal.,2007; Tadićetal.,2012a; Tadić*etal.*, 2012b).

Effectsonmonoaminergic-mediatedneurotransmission

In 2005 Knörle and Schnierle published a patent application, where the inventors claimed that plants ofthe genus Sideritis for preventing and influencing disorders associated with altered serotoninergicneurotransmission; these include depressive disorders, chronic pain, panic attacks, generalized anxietydisorder, obsessive-compulsive disorder, climacteric complaints and eating disorders such as bulimia.(Knörle and Schnierle P. 2005). They extended that study to the effects of Sideritis ssp. on othermonoamines, including serotonin, noradrenaline, and dopamine uptake in rat brain synaptosomes andhuman choriocarcinoma JAR cells line (Knörle, 2012). The water and alcoholic Sideritis species extractsinhibited the uptake of monoamines into rat brain synaptosomes by their corresponding transporters intheEC5030-40µg/mlrange.Inhibitionofthe humanserotonintransporterbytheextractwasevenmoreeffective (EC50 1.4 µg/ml), suggesting their potential use in mental disorders associated withmalfunctioning monoaminergic neurotransmissions, such as anxiety disorders, major depression,attention-deficit hyperactivity disorder, cognitive impairment or neurodegenerative diseases (Knörle,2012).Theseresultswere unrelatedtothedistinctusedSideritisspeciesnoroftheir origin.

Further studies were conducted with pharmaceutical Quality grade ethanolic-water *S.scardica, S.raiseri,and S.euboea*extracts preparation and aqueous tea-analog preparation (nutrifn®mental)*in vivo* study inmice to detect psychopharmacological effects assessed by their brain electrical activity recorded byElectro EncephaloGraphic Phraseogram (EEGP) (Walbroel andFeistel, 2010; Walbroel andFeistel, 2011;Feistel and Walbroel, 2011, Dimpfel 2013). Stereotactic implantation of four semi-microelectrodes intorats' frontal cortex, hippocampus, striatum, and reticular formation allowed continuous wirelessmonitoring of field potentials (EEG) before and after drug intake. After frequency analysis (Fast FourierTransformation), electric power was calculated for six ranges (delta, theta, alpha1, alpha2, beta1, andbeta2). The most substantial effects were observed in alpha2 waves, which are related to an activation ofdopaminergic neurotransmission; delta, theta, and alpha1 waves were also attenuated, suggesting theactivation of the cholinergic, norepinephrinergic, and serotonergic transmission systems. All activitieswere located in the frontal cortex and hippocampus regions responsible for cognitive performance(WalbroelandFeistel, 2011;Dimpfel,2013).Allextractsweregivenorallybygavagedissolvedordispersed

in water (1 ml/kg weight). The dose of *S.scardica*extract (extraction solvent – 20 % ethanol, DER 5–9:1,containing0.5–1.5% flavonoids, 0.1–0.4% caffeoylquinic acids, Finzelberg GmbH & Co. KG, D 56626Andernach, Germany) corresponded to a recommended human dose of 800-1200 mg. Dosages werechosen by considering the human dose recommendation and a relationship factor of 5–10:1 based onkilogrambodyweight(Dimpfel,2013).

*Sideritisscardica*water extract (10% polyphenols including 1.4% flavonoids) protected scopolamine-induced memory impairment and anxiety-like behavior in male albino IRC mice (Lazarova et al., 2023).The plantextract wasorallyadministeredinthedaily dose of6000mg/kg(correspondingto 30g ofhuman dose) for 11 consecutive days in the presence or absence of scopolamine (1 mg/kg, i.p). In theseexperiments,the*Sideritisscardica*waterextractpreventedattenuatingofnoradrenalinandserotoninlevelsi n the brain of mice with scopolamine-induced neurodegeneration in the dementia model however didnotaffectscopolamine-reducedacetylcholinesterase activity(Lazarova et al.,2023).

Overall, *Sideritisscardica*hydroalcoholic extracts inhibit neurotransmission of serotonin, noradrenaline,anddopaminesuggestingpotentialuseinmentaldisorderssuch asanxietydisorders,majordepression,attention-deficit hyperactivity disorder, cognitive impairment, or neurodegenerative diseases (Knörle,2012;Feistel and Walbroel,2012).

Effectsonamyloid-βtriggeringneurodegeneration

ThemainfeatureofAlzheimer'sdisease(AD)isaprogressivelossofmemoryandcognitiveabilities.Thecrucial pathogenic step of neurodegeneration and progression of AD is amyloid- β (A β) deposition as aneuritic and extracellular diffuse plaque, intracellular tau protein in the form of neurofibrillary tangles,andbrainatrophy.

Daily oral treatment with dried ethanol 20% extracts of *Sideritisscardica*, and *Sideritiseuboea,* as well astheir 1:1 combination (Finzelberg GmbH & Co. KG, Andernach, Germany), enhance memory andlearning in Alzheimer's disease (AD) induced amyloidosis mouse models in APP-transgenic and agedC57Bl/6 mice (Hofrichter et al., 2016). The raw herb material (residual humidity of < 12%) was extractedexhaustively using ethanol 20% (v/v); the solvent was evaporated *in vacuo* up to a soft viscous extract,dried with a carrier (70% native extract, 30% maltodextrin), milled to a fine powder extract, re-suspendedin water and applied by daily gavage at the age of 40 days (AD-initiation) or 50 days (post-AD onset),respectively,uptotheage of100days.(Hofrichteretal.,2016).Theextractswereappliedintwodosages: 1.2 g/kg body weight (AD initiation) and 12 g/kg body weight (post-AD-onset). Non-transgenic micewere treated for 15 days (short-term) with an intermediate dosage of 6 g/kg body weight of the Sideritisextract combination, starting at the age of 135 days for 15 consecutive days until the age of 150 days (firstperiod), and repeatedly for three further periods of 15 days at ages 300, 450, and 600 days, respectively(Hofrichter et al., 2016). Sideritis spp. extracts improve memory performance in APP-tg mice;improvesretentiveness,learningaptitude,anddecreasedescapelatencyvaluesof micetreatedpost-AD-onsetwithSideritisspp.extractsincomparisontovehicle-treatedcontrolmiceindicateincreasedspatialmemory. Theimprovementofcognitionfunctionswasassociatedwithhistomorphologicalandbiochemical changesrelatedtothedepositionofsolubleamyloid-β(Aβ),whichrecognizedtriggersofthedisease.ThetreatmentwithSideritisscardicaextractsstronglyreducedAβ42l oadinmice, accompanied bythe increased phagocytic activity of microglia, increased expression of the α-secretase, and fully rescuedneuronallossofmicetonormallevelsbyaffectingAβpathologyandcognitivedecline(Hofrichteretal.,2016).

In another study, the neuroprotective activity of hydroalcoholic extracts of S. scardica (prepared fromwater,20,40,50,70%ethanol,andunipolarfractionswerepreparedfromthe40%ethanolicextract; FinzelbergGmbH&Co.KG,Andernach,Germany) hasbeendemonstratedin*Caenorhabditis elegans* nematode used as a model for Alzheimer's disease associated with amyloid-β aggregation andtoxicity (Heiner et al. 2018). The exposure of the extracts in transgenic *C. elegans* strains expressingamyloid-β resulted in a reduced number of peptide aggregates in the head region of the worms. Italleviated the toxicity of amyloid-β, evident through the intensity of paralyzed animals. The 40 and 50%ethanol extracts were the most active, decreasing the plaque number by 21% and delaying the amyloid-β-inducedparalysisbyup to3.5h(Heineret al. 2018).

*Sideritisscardica*methanolic extract exhibited beneficial effects against amyloidogenic and Taumisprocessing pathways in Alzheimer's Disease neuronal cell culture models, including the humanneuroblastoma overexpressing SH-SY5Y-AβPP and the hyperphosphorylated tau expressing ratpheochromocytomaPC12-htaucellsviadecreasingtheactivationoftheGSK3β,ERK1,andERK2kinasesof tau, and by tau hyperphosphorylation. The extracts appear to promote AβPP processing through thealpha, non-amyloidogenic pathway suggesting that*S. scardica*can prevent or inhibit the progression ofAD(Chalatsaet al., 2018).

Recently Ververis et al. 2023 compared the neuroprotective activity of eight fractions of *Sideritisscardica*water extract in SH-SY5Y human neuroblastoma cells treated with highly neurotoxic amyloid Aβ25–35peptides. Four of the eight fractions statistically inhibited neurotoxicity;the most active was initialaqueousextractinconcentrationsof50–200μg/mL,characterizedasrichesofneuroprotectivesubstances,suchasapigenin,myricetin-3-galactoside,andellagic acid(Ververisetal.,2023).

NeurogenicActivity.

Theneurogenicpotentialof*Sideritisscardica*arealpartwaterinfusionwasfoundaspotentasaclassicalneuronal inducer, the combination of retinoic and valproic acid (c = 10/50 μM, positive control),promotingthegenerationofnewneurons,assessedby differentiation-inducingandnormalized *Renilla* activity assays in mouse embryonic forebrain cells (Tumou et al., 2023). Concentration-dependent studyofcytotoxicityofeighthSideritisssp.driedinfusionswasfoundIC50intherangeof163to322μg/mL inthrice-subcloned SH-SY5Y cell line culture derived from the SK-N-SH neuroblastoma cell line, which arewidelyusedasamodelforneurodegenerativediseases.TheIC50 cytotoxicconcentrationof*Sideritis scardica*was 320 μg/mL. Metabolomic fingerprinting of eight analysedSideritis taxa using showed thatphenylethanoid glycosides (trans-verbascoside and trans-leucosceptoside A) and flavonoid glycosides(isoscutellarein 7-O-[6‴-O-acetyl- β -D-allopyranosyl]-(1 → 2)- β -D-glucopyranoside andapigenin 7-O-[6″-O-trans-p-coumaroyl]- β -Dglucopyranoside) are presumably principal components of the genusSideritissuggestingthattheycontributefortheeffectonthecellviabilityofSH-SY5Yneuroblastomacells(Tumouetal., 2023).

Antimicrobialproperties

Various *Sideritisscardica*Griseb. extracts and their fractions have been studied for its antimicrobialpropertiesagainstGram-positivebacteria,*Streptococcuspyogenes,Streptococcuscanis,Moraxellacatarrhalis,Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus,* methicillin resistant *Staphylococcusaureus, Corynebacterium pseudotuberculosis, Enterococcus faecalis*, Gram-negative bacteria *Escherichia coli,Pseudomonasaeruginosa,Klebsiellapneumoniae,PasteurellamultocidaandHaemophilussp.*,andyeast*Candida*

albicans. The strong to moderate antimicrobial activity of all investigated extracts was demonstrated in theminimal inhibitory concentration in the range from 40 to 2.56 µg/ml. Maximum activity was observedagainst *S. epidermidis*, *M. luteus*, *E. coli*, and *P. aeruginosa*, and moderate activity against *K. pneumonia*. Theantimicrobial activity of the extracts was similar regardless of differences in their chemical compositions(Tadićetal.,2007;Tadićetal.,2012a; Yaneva& Balabanski, 2013).

Gastroprotectiveandinflammatoryeffects

Gastroprotective and inflammatory effects of the ethanol, diethyl ether, ethyl acetate, and *n*-butanolextracts of *Sideritisscardica*were studied in ethanol-induced acute gastric damage in rats in the doses of50–200 mg/kg (*p. o.)*using ranitidine (5–20 mg/kg, *p. o.*)and indomethacin (4 mg/kg, *p. o.*), as referencedrugs. All examined extracts produced dose-dependent gastroprotective activity with an efficacycomparable to that of the reference drug ranitidine. Diethyl ether and *n*-butanol extracts reduced the ratpaw edema in the doses of 100 and 200 mg/kg (to 53.6 and 48.7 %; 48.4 and 49.9 %, respectively)comparablytoindomethacinreducing50%effect (Tadić*et al.*,2012b).

Secondarypharmacodynamics

Antioxidantactivity

*Sideritisscardica*extractswere comparedwith*Sideritissyriaca*,*Sideritismontana*extracts,andtworeferenceantioxidants - hydroxytoluene (BHT) and rosmarinic acid by the β-carotene bleaching test (BCBT) and2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging test. The most potent antioxidant effect wasobserved for the apolar extracts similar to that of BHT in the β-carotene bleaching test. In contrast, thepolar extracts and rosmarinic acid were less potent than that of BHT. The inhibition of hexanal formationin bulk safflower oil by Sideritisscardica extracts was as efficient as BHT but less so than rosmarinic acid.The radical scavenging effect of butanol, ethyl acetate, and methanol extracts of Sideritis extracts againstDPPH-induced oxidation was similar to that of rosmarinic acid (Koleva et al., 2003). The DPPH-inducedradicals scavenging assays revealed that *Sideritisscardica*and others Sideritisssp (*Sideritisclandestina*subsp. *clandestina, Sideritiseuboea, Sideritisperfoliata*subsp. *perfoliata, Sideritisraeseri*subsp. *raeseri,* and*Sideritissyriaca*) extracts exhibited substantial antioxidant activity (% inhibition >74 at 300 µg/ml)(Papaefstathiouetal., 2014).

The antioxidant potential of *Sideritisscardica*extract was compared *Camellia sinensis* extract in HepG2cells.The*S.scardica*freshleaves(extractionsolvent - 70%methanolat70◦C,DER8:1;Indena,Milan,Italy)wasspecifiedbythemanufacturerascontainingapolyphenolcontent of75±5%,anEGCGcontentof30 ±5%;contentofothercatechinsof40±100%gandacaffeinecontent<8%(Danesi etal.,2012).AlthoughSideritisscardica extract had a lower phenolic concentration and total antioxidant capacity than *Camelliasinensis* extract, their cellular antioxidant effects were similar. The different phenolic pattern of theextractssuggeststhattheprotectiveactivityisnotlimited tocatechins(Danesietal.,2012).

Anti-agingeffects

The anti-aging potential of *Sideritisscardica*was compared with *Plantago major* and propolis extractsproduced by so-called Natural Deep Eutectic Solvents (NADES) in lifespan experiments in fourSaccharomycescerevisiaeyeaststrains-awildtypeandthreechromatinmutantsexhibitingcharacteristics

ofprematureaging.Theextractamelioratestheircellulargrowthandcellcycleandinfluencestheactivityofsomes tress-responsivegenes.(Vasileva et al., 2022)

About 6000 plant species growing in Greece were selected to identify plants that can delay cellularsenescence by regulating age-related signaling pathways in senile skin, which is characterized bysubstantial alterations in collagen, hyaluronan, and elastin and strongly affected exposure to sunlight.More than 440 plant extracts were screened and evaluated for their antioxidant and anti-melanogenicproperties as a preferable source of photoprotective agents against skin hyperpigmentation. The mostpromising 4% of the extracts were chemically and pharmacologically characterized in vitro and cell-basedassays coveringmostof theparameterscontributingtoskinaging.In particular,the methanolicextractsof *Sideritisscardica*and *Rosa damascena*showed promising effects against specific targets involved in skinaging(Sklirouetal.,2021).

Cytotoxicactivities

Cytotoxic potential of ethanol, diethyl ether, ethyl acetate, *n*-butanol extracts of *Sideritisscardica,* andmajor phenolic compounds of the extracts was studied in PBMC, B16 melanoma, and HL-60 leukemiccells. Only diethyl ether extract triggered significant dose-dependent cytotoxicity in B16 cells and HL-60cells, decreasing cell growth to 51.3% and 77.5% of control, respectively, when used at 100 µg/ml. Themain cytotoxic flavonoids were luteolin, apigenin-7-0-ß-glycoside, apigenin, and luteolin-7-0-ß-glycoside.(Tadićetal*.,* 2012b;Jeremicet al*.,* 2013).

Anti-obesityandanti-diabeticproperties

A study of the effects of *Sideritisscardica*aqueous extract on metabolic disorders induced by ovariectomyin rats aimed to assess their food intake, weight gain, body composition, fasting glucose levels, responseto oral glucose challenge, liver glycogen content, catalase activity, thiol groups, malondialdehydeconcentrations, as well as AMP-activated protein kinase activity in liver cells. Administration of *S.scardica*extract(200mg/kgdailyfor24weeks)loweredblood triglycerides, reduced fastingglucose levelsand blood glucose peaks after oral glucose challenge, increased liver glycogen content, and significantlyhighercatalaseactivityand thiolgroupconcentration inovariectomizedrats.Theauthorsconcludethat
S. scardica extract attenuates metabolic disturbances in rats suggesting possible therapeutic benefits fordiabetes,obesity,andpostmenopausalwomen,withincreasedriskforbreastandendometrialcanceranda riskfor cardiovascularand thromboembolicdisease(Jeremicetal.,2019).

Pharmacokinetic

The primary aim of pharmacokinetic studies of herbal preparations comprising multi-componentintervention is to trace their absorption and distribution in body tissues, metabolism, and eliminationafter oral administration to estimate concentrations matching effective concentrations found inpharmacodynamicstudies.
Metabolism of polyphenols and their urine excretion was studied in 10 healthy human subjects aftersingle-dose administration of 8 g *Sideritisscardica*decoction 300 mL of Herba Sidetiris decoction. Thirty-onemetabolitesofhypolaetin,methyl-hypolaetin,isoscutellarein,methyl-isoscutellarein,apigenin,and32phenolic acid metabolites were quantitatively analyzed by a validated by HPLC-DAD-ESI-MS/MSmethod. In a total of 63 glucuronides and sulfated metabolites of flavonoids (hypolaetin,
isoscutellaerin,andapigenin)derivativesandhydroxycinnamicacidderivatives(quinic,caffeic,chlorogenic,ferulic,and

coumaric acids) were identified in excreted in human urine collected for 24 h after oral administrated 300mLof Herba Sidetirisdecoction(PetreskaStanoevaandStefova, 2013)

Acomparisonofthecompositionofhydroxycinnamicacidderivativesof Sideritisdecoctioncontainingonly four hydroxycinnamic acid derivatives, with their urine excretion, showed the presence of 32hydroxycinnamicacidmetabolites(5 quinicacidderivatives,five caffeicacidderivatives,seven caffeoylquinic acid derivatives, eight ferulic acid derivatives, three dimethyl ferulic acid derivatives, threeferuloyl quinic, acid derivatives, and two coumaric acid derivatives, presumably due to interactions withtheintestinaland/or hepaticdetoxificationenzymes.

Thetotalcontentofphenolicmetabolitesinurinesampleswasdeterminedasasumofthetotalcontent ofmetabolites from hydroxycinnamic acid derivatives, apigenin, hypolaetin, and isoscutellarein. The totalamountofhydroxycinnamicacidderivativesinurinesamplesrangedfrom1.714to33.62 µmol,which corresponds to 5.24–18.18% (n/n) of total metabolites excreted in urine and around 1.5% of the ingesteddoseoftotalphenolicspresentin300mLoftheSideritisdecoction.Total metabolitecontentinurineafter24 h was in the range from 32.73 to 184.9 µ mol, which represents 1.46–8.24% (n/n) of the total phenoliccontent present in the 300 mL of Sideritis decoction ingested. The most abundant urinary metaboliteswere methyl-hypolaetin and methyl-isoscutellarein glucuronides, excreted mainly from isoscutellareinandapigenin(PetreskaStanoevaand Stefova,2013).

Furtherstudiesarerequiredtoestimateactivedosesandbloodconcentrationsofprinciplecompoundsof GMT or their metabolites targeting the body tissues in matching effective concentrations, particularlycrossingtheblood-brainbarrier.

Preclinicalsafety

Acuteandrepeated-doseoraltoxicity

A Sideritis herb dry extract (70% native, 30% maltodextrin; extraction solvent: 20% V/V ethanol) has beentested in an acute and repeated-dose oral toxicity study in Sprague Dawley rats (Feistel et al.2018;EMA/HMPC/39455/2015). No gross or histopathological abnormalities and no signs of toxicity ormortality could be detected in all six female rats throughout the study period of 14 days when treated atthe dose level of 2000 mg/kg of the test item. The tested Sideritis herb extract has been assigned tocategory 5, covering the range for oral LD 50 to be 2000 mg/kg- 5000 mg/kg body weight. The repeated-dosetoxicity oftheextract wasstudiedbyitsdaily oraladministrationofratsbygavageindosagesof250mg/kg, 500 mg/kg, and 1000 mg/kg body weight for 28 days, followed by a 14-day recovery period andcompared to the control groups having received distilled water only. Additionally, doses of 0 mg/kg and1000 mg/kg were used to investigate the reversibility of possible delayed occurrence of symptoms. Nomortality or changes in body/organ weight or food consumption have been observed. The sensoryreactivity of auditory, visual, and proprioceptive stimuli did not show abnormalities in the treatment andcontrol groups. Hematological analysis also revealed no abnormalities except for an increase of the MCVand MHCH values at the dose of 1000 mg/kg in males and the case of platelets at 1000 mg/kg in femalerats. A statistically significant decrease was documented for the values of total WBC at the dose of 500mg/kg, male) and MCHC (500 mg/kg, female) in male and female rats treated with different doses of thetest item; however, the changes were only marginal. No hematological changes have been caused by theSideritis extract, except for a decrease of MCH in female animals from the 1000 mg/kg reversal groupsacrificed on day 43 but estimated to be in the biological range. Concerning the clinical, biochemicalparametersofCalciumandsodium(250mg/kg,500mg/kg,and1000mg/kg,male),Chloride(250g/kg

and 1000 mg/kg, female), and Sodium (500 mg/kg and 100 mg/kg, female) have been marginallyinfluencedbythetestitem.Theorganweightofthetestedratsfromdifferentdoseandcontrolgroupsand thatof the reversalgroup (1000mg/kg) didnotdiffer.
Moreover,thepathologicalandhistopathologicalexaminationsdidnotindicateanyabnormalitieswhichcould be referred to the treatment with the Sideritisscardica dry extract. The extract's no-observed-adverse-effect level (NOAEL) was determined at 1000 mg/kg body weight in male and female animalswhen the Sprague Dawley rats were treated over 28 days in this repeated dose oral toxicity study. Thestudy reveals no toxicity of S. scardica, supports its favorable safety profile, and confirms theacknowledgedtraditionalmedicinaluse inhumans(Feisteletal.2018).

In a recent study of subchronic toxicity of dry hydromethanolic (70%) extract of *S.scardia*(totalpolyphenols, 88.66±2.57 mg GAE/g; total flavonoids, 22.01±1.23 mg QE/g; Vesselino Ltd. Kazanlak,Bulgaria), the powdered extract was orally administered to male Wistar rats for 12 weeks at daily doses of100, 200, and 400 mg/kg (Yanchev et al., 2023). The subchronic toxicity experiment follows up an acutetoxicity assessment in which no lethality was observed after a single oral administration of doses of 1000,2000, 5000, and 10000 mg/kg. All hematological and biochemical results remained within the normalreference ranges described for the species. All hematological, biochemical, and histological examinationsshowed no abnormalities including the morphology of the examined organs (brain, stomach, liver, andkidney).

Genotoxicity
FourAmestestswiththedryextractsfrom*Sideritisscardica*herbofdifferentpolarity(water;20%(V/V)ethanol; 50% (V/V) ethanol; n-heptane) have been evaluated for their genotoxic potential(EMEA/HMPC/67644/2009;EMA/HMPC/39455/2015).
FourAmes testswiththedryextractsfrom*Sideritisscardica*herbofdifferentpolarity:

a. 70%native,30%maltodextrin;DERnative:4-8:1;extractionsolventwater,
b. 70%native,30%maltodextrin; DERnative:7.2:1;extractionsolvent20%(V/V)ethanol,
c. 70%native,15%maltodextrin,15%silica;DERnative:6:1;extractionsolvent50%(V/V)ethanol,
d. 50%native,50%silica;DERnative:83:1;extractionsolventheptane

All four extracts have been tested in the Salmonella typhimurium strains TA 97a, TA 98, TA 100, TA 1535,and TA 102 with and without metabolic activation. The results of Ames tests conducted on all fourextracts of different polarities were negative (Feistel et al.2018). The water Sideritis extract (a) did notcause gene mutations by base pair changes or frameshifts in the genome of the tester strains used, andtherefore, the test item has been considered not to be mutagenic (EMA/HMPC/39455/2015). The studyreveals no concerns about the mutagenic effects of all four extracts a-d covering the entire spectrum ofphytochemical constituents of the Sideritisscardica herb, including polar and non-polar constituents.(Feistelet al.2018).

Carcinogenicity
Nocarcinogenicitystudies havebeencarriedoutonSideritisscardicainthescientificliterature.

Reproductiveanddevelopmentaltoxicity
NoreproductiveanddevelopmentaltoxicitystudiesonSideritisscardicawerefoundinthescientificliterature.

Clinicalpharmacology –clinicaltrials

Cognitiveandanxietydisorders

Neurodegeneration-associated cognitive disorders, including Alzheimer's disease and mild cognitiveimpairments (MCI, regarded as a transitional stage of Alzheimer's disease), primarily affect memory,learning, concentration, and perception performance (Shah et al., 2000; Janoutová et al., 2015; Fiorini,etal.,2020).Anxietycanalsocausecognitivedisorderssymptoms,suchasdifficultyconcentrating,fatigue,increasedheart rate,and othersymptoms.

Recent clinical studies aimed to assess the efficacy of several preparations of *Sideritisscardia*on thecognitive function of healthy individuals in a stressful environment (Behrendt et al., 2016) and elderlyadults with MCI and anxiety (Dimpfel et al., 2016a; Dimpfel et al., 2016b; Wightman et al., 2018). Inaddition to the cognitive performance, the patient's mood, cerebral blood flow, blood pressure, and brainelectricalactivity werestudiedindetail.

Cognitivefunctionsofhealthysubjectsinstress.

Anherbalextractof*Sideritisscardica*(330mgofanalcoholicaqueousextract,Schaper&BrümmerGmbH& Co. KG, Salzgitter, Germany), vitamin B1 (0.55 mg), vitamin B6 (0.7 mg), Vitamin B12 (1.25 µg), andfolic acid (100 µg) was studied in an open-labeled trial in 64 healthy 25-60 years old participants takingthesupplementorally twice dailyfor six weeks(Behrendtetal., 2016).

The study aimed to assess the efficacy of a fixed combination of *Sideritisscardica*with vitamin B complexto reduce stress-induced impairment of working memory, cognitive flexibility, and controlled behaviorandimprove stresstolerance.Thecognitiveperformanceofhealthysubjectswasassessedbytheso-calledTrail-Making test (TMT), by concentrating their attention and short memory by linking randomlyscatterednumbersandalphabeticcharactersandtheColor-Word-Test(CWT,*syn.*Stroop-Test)beforeand after an acute stress stimulus, including noise and mental load (CWT) interference. The validatedPerceived Stress Questionnaire (PSQ) was also used to assess the subjective chronic stress perception onemotional and cognitive levels in the study participants. TMT was not feasible for measuring anyintervention's stress-relieving or attention-promoting properties because the intra-assay controls did notcomply with the assumptions concerning the accuracy of this test. In contrast, the CWT and PAQ provedsuitable for assessing the influence of stress-induced impairments; CWT reaction time after six weeks ofproduct intake was better than at baseline, without an increase in the error rate. Stressor-induced, i.e.,noise-induced and color-word-interference-induced impairments of CWT reaction times improved uponproductintake.

The authors concluded that dietary supplementation of Sideritisscardica with vitamin B can alleviatestress-inducedimpairment,improvingworkingmemoryandcognitiveflexibility.(Behrendtetal.,2016).The authors suggested that the combination of *Sideritisscardica*with vitamin B may be relevant forpersons solving cognitive tasks under conflict and/or noise (e.g., open-plan offices or car-driving) andsupport that the tested product alleviates stress-induced impairment of executive functioning (workingmemory,cognitive flexibility,controlledbehavioralinhibition) (Behrendtetal.,2016).

The study limitations include the lack of a placebo group or blinding since a study design without acontrol group is often deemed insufficient for formal proof, which can be achieved by arandomized, double-blind,controlledtrial.

Cognitivefunctionsofelderlypatientswithmildcognitiveimpairments.

Two publications described a study of *Sideritisscardica*of dry extract (extraction solvent – 20 % ethanol,DER 5–9:1, containing0.5–1.5% flavonoids 0.1–0.4% caffeoylquinic acids), and its combination with*Bacopamonnieri*extracts(memoLoges®,Dr.LogesGmbH,Winsen,Germany)inelderlyadultswithmildcognitive impairments(Dimpfelet al.,2016a;Dimpfel et al.,2016b).

Acute effects of a single dose of 500 mg of *Sideritisscardica*of dry extract and its combination with *Bacopamonnieri*extracts (160 mg, 320 mg, and 480 mg) were studied in an open-labeled, placebo-controlled,crossover design trials in 10 patients of 61.88 ± 6.69 years old (Dimpfel et al., 2016a), while the effect ofmultiple of administration of the combination of 500 mg of Sideritisscardica of dry extract and itscombination with *Bacopa monnieri*extracts (160 mg, 320 mg, and 480 mg) were conducted in randomized,placebo-controlled, 2-armed trial with parallel design crossover trial in 32 (58.63 ± 5.79 years old) patients(Dimpfel et al., 2016b). The included patients were diagnosed as MCI by the questionnaire "DemTect"using 18 point dementia scale in the range from 8 scores (severe dementia) to 13 scores above ("normal"cognitiveperformance).
Efficacymeasureswereassessedbyquantitative EEGrecordingandpsychometric tests,including:

- Theso-called"paper-pencild2-test"oftheabilitytoconcentrate,whenthepatientshavetomarkall "d" spellings letters with two adds for 20 seconds in each line under the condition of EEGrecording.
- The "concentration-performance-test" (CPT) targets the performance of arithmetic when thepatientsmemorizethetransitoryresultsofthefirsttasktobeprocessedaftertheperformanceofthese condtask.
- The memory test memorized a combination of numbers and spellings for 4 seconds (e.g.,Dv8L3oPX). The order of symbols has to be remembered, followed by a time of 10 secondsduring which the screen remained dark, and a four-fold multiple choice, including the correctanswer, was presented for decision. The number of tasks and % correctness were evaluated toevaluate as aperformanceindex.

Single dose effect of *Sideritis*extract alone or in combination with *Bacopa* extract (memoLoges®) led tostatistically significant improvement in concentration increasing the attention of patients in the d2-concentration test. Quantitative EEG spectral maps recorded under the different experimental conditionsdisplayed enormous differences between both extracts. Sideritis extract and its combination with a lowamount of Bacopa extract (160 mg) induced increasing spectral power in frontotemporal brain areascompared to placebo. A different activity of both extracts was confirmed by discriminant analysis(Dimpfelet al. 2016a).

The effect of multiple administrations of the combination of *Sideritisscardica*and *Bacopa monnieri*extract(memoLoges®) in patients with MCI for four weeks was similarly assessed by psychometric tests (d2-concentrationtest,arithmeticcalculationtest,andamemorytestand QuantitativeEEGrecording
on the first day and one day after the last repetitive administration.Intake of memoLoges® induced atrend of improvement of performance in all three psychometric tests suggesting that a combination of*Sideritisscardica*and *Bacopa monnieri*extract can improve concentration and short memory.EEG dataanalysis revealed attenuation of delta and theta spectral power in the frontal brain similar to as reportedin the EEG pattern of the Alzheimer drug rivastigmine, "normalizing" the spectrum. The combination
of*Sideritisscardica*and*Bacopamonnieri*statisticallysignificantlyincreasedbetapoweronthebackgroundofmentalload,suggestinga positive effectinMCIpatients.(Dimpfel etal. 2016b).

Effectonmemory,attention,moodandcerebralbloodflowinanxietyofelderlyadults

A clinical trial of GMT in 50–70-year-old healthy adults given standardized tests for cognitive function,mood and cerebral blood flow, significantly improved anxiety state, brain circulation, working memoryand raised visual sustained attention. (Wightman et al., 2018). Exclusion criteria were high bloodpressure, history of neurological, vascular or psychiatric illness, current diagnosis of anxiety ordepression,andanyhealthconditionthatwouldpreventthefulfillmentofthestudyrequirements. AfinaldatasetofN=140wasarrivedatforthecognitiveanalyses.Datacatchmenterrorsresultedinasampleof N=142 forthemood (StateTraitAnxietyInventory (STAI))analysis.

The aim of the randomized, double-blind, placebo-controlled, parallel groups trial was to assess theefficacy of *Sideritisscardica*dry extract in two daily doses of 475 mg and 950 mg compared to activecontrol (*Ginkgo biloba* extract, daily dose 240 mg),and placebo on the cognitive performance, mood,cerebral blood flow, and blood pressure in 155 subjects following acute administration(single dose atDay 1) and repeated administration (two capsules daily, one in the morning, advised "with breakfast,"andonecapsuleintheeveningadvised"witheveningmeal")forfourweeks(anaccumulativeeffectof28days of treatment on Day 28). *Sideritisscardica*dry extract was specified for 6.25% phenolic contentcontaining 0.5% caffeoyl quinic acids, 0,4% acteoside, 1,5% flavonoids, 1.25%, including scutellarin,apigenin,luteolin,etc.andtheirglycosides,extractionsolvent-20%ethanol(FinzelbergGmbH&Co. KG,MartinBauerGroup,Germany).

The cognitive functions were assessed using the “Computerized Mental Performance AssessmentSystem”, comprising:

- Speed(msecs)andAccuracyofEpisodicMemory(%correct),derivedfromoutcomemeasures ofindividual cognitive tasks including Delayed word and Pictures' Recognition, and DelayedName/Face and WordRecall.
- WorkingMemory(%correct),deliveredfromoutcomemeasuresofindividualcognitivetasksinclu ding Numeric Working Memory and Cognitive Demand (working memory executivefunction attention) battary including Rapid Visual Information Processing (RVIP) and BondLader VisualAnalogScales(VAS).
- Speed(msecs)andAccuracyofAttention(%correct)-ChoiceReactionTimetask.

Moodoutcomesmeasureswereassessedby theBond-LadermoodandtheState-TraitAnxietyInventoryduringthe training and screeningvisitstoprovide abaselinemeasureofmood.
The blood pressure readings and cerebral blood flow were monitored using a frequency domain"quantitative" Near-Infrared Spectroscopy system, providing absolute measurements of oxygenatedhemoglobin (HbO2), deoxygenated hemoglobin (HHb), total hemoglobin (tHb; HbO2 + HHb)
andoxygensaturation(Ox%;HbO2/tHb×100%)forquantifyingacutechangesinhemodynamicresponseinCer ebralcirculationflowandoveranextendedperiodbetweenDay1 and Day28.

Compared to the group given a placebo and active comparator group given, the patients that receivedofGMTobserved the followingimprovements:

- Improved mood and Reduced anxiety state, Mood—State-Trait Anxiety Inventory (STAI):GMT,950mg/475mgvsplaceboandGingko,singleeffectonDay1andrepeatedadministration for4weeks
- Greaterabilitytorecognizepictures(%correct):GMT,950mgvsGingko,singleeffectonDay1and repeatedadministrationfor 4 weeks
- Enhancedinformationprocessing(ProcessingFalseAlarms(number):GMT,950mgvsplacebo,repea ted administrationfor4weeks

- Increasedreactionspeed (SpeedofAttention(milliseconds):GMT,950mg/475mgvsGingko,singleeffectonDay1 and repeated administrationfor4weeks
- Greaterabilitytoremainfocusedandaccessworkingmemory,
- Improvedoverallcognitiveperformance,
- Increasedtransport ofbloodoxygenfromthelungstoallotherbodytissues,includingthebrain.
- Improved blood flow to the brain's prefrontal cortex—the part of the brain associated withcognitivebehavior,personalityexpression,decision-making,andappropriatesocialbehavior.

The most evident effects of GMT in the daily dose of 950 mg, compared to placebo were improvement ofcognitivefunction,significantlyreducingfalsealarmsinrapidvisualinformationprocessingtestafter28days oftreatmentandreductionofanxietycompared toGingkoandplacebo.
Both doses of GMT revealed significantly greater oxygen saturation increasingoxygenated haemoglobin(Ox%) in the prefrontal cortex during completion of cognitively demanding tasks on Day 1 with thelower, 475 mg dose, producing the most pronounced effect, while Ginkgo was associated with lowersaturation.Thehigherdose correspondinglyshowedgreaterlevelsoftotalanddeoxygenatedhemoglobinon Day 1 but no further effects were seen on cerebral blood flow after repeated administration for fourweeks.SurprisinglysingledoseeffectofGinkgodecreasedlevelsofOx%andincreasedlevels ofHbanddecreasedlevelsofbothHbOandTHbafter treatmentforfourweeks.

Theauthorsconcludethatsignificantlyimprovedcognitiveperformancefollowing GMTonDay1couldbe due to significant modulation of the cerebral blood flow response, while the improvements ofcognitive performance on Day 28 are likely to be due to the decreases in state anxiety, suggestingpromotingtounderpinmore prolongedcognitive improvements(Wightmanetal.,2018).

Theriskbiasandqualityscores
The risk bias and Quality scores of two available randomized placebo-controlled trials assessed byCochrane (Higgins et al., 2011), Jadad (Jadad et al., 1996), and CONSORT (Gagnier et al., 2006) criteria areshowninTable 1below.

Table1here.

Conclusions.

Preliminary studies have indicated that GMT may enhance memory and cognitive function, improvingattention, focus, and overall mental performance. Recent research has revealed that GMT contains avariety of bioactive compounds, which have been linked to mental enhancement, improvements incognitiveperformance,andneuroprotectiveeffects,potentiallyreducingtheriskofage-relatedcognitivedeclineand neurodegenerative disorders,

Clinicalassessmentofherb-druginteraction

Drug - Consumption of the aerial parts of *S. scardica*decoction is unlikely to result in herb-druginteractionsinvolvingtheenzymesstudied,exceptforpotentialherb-CYP2A6substrateinteractioninmales(Begasetal., 2018).

Adversereactions

None known (EMA/HMPC/39453/2015). If adverse reactions occur, a doctor or a qualified healthcarepractitioner should be consulted.

Contraindications

Hypersensitivitytotheactivesubstanceandotherplantsofthe Lamiaceae(Labiatae)family(EMA/HMPC/39453/2015).

Warnings

The use in children and adolescents under 18 years of age was not established due to a lack of data. If thesymptomsworsenduringtheuseofthemedicinalproduct,adoctororaqualifiedhealthcarepractitionershould be consulted(EMA/HMPC/39453/2015).

Precautions

Pregnancy,fertility,andlactation

Safety during lactation and pregnancy has not been established. Without sufficient data, use duringpregnancyandlactationisnotrecommended.Nofertilitydata areavailable.(EMA/HMPC/39453/2015).

Pediatricuse

Due to the lack of safety data, the crude drug should not be used in children under the age of 12 years.(EMA/HMPC/39453/2015).

Interactions with other medicinal products and other forms of interaction and otherprecautions

No information was found. (EMA/HMPC/39453/2015). Consumption of the aerial parts of *S. scardica*decoction is unlikely to result in herb-drug interactions involving the enzymes studied, except forpotentialherb-CYP2A6substrateinteractioninmales(Begasetal.,2018)

Dosageforms

Comminuted herbal substances, teas, dried hydroalcoholic or aqueous extracts, capsules, and otherGalenical preparations for internal use. Store in a well-closed container (EMA/HMPC/39453/2015;Wightmanet al., 2018).

DeclarationoftheherbalmedicinalproductintheSmPC.

Each capsule contains 450 mg of extract (as a dry extract, refined) from SideritisscardicaGriseb., folium(equivalent to 2.25 g – 4.05 g of *Sideritisscardica*, DER 5–9: 1), corresponding to 6.25% polyphenolsincluding 0.5% caffeoyl quinic acids, 0,4% acteoside, 1,5% flavonoids, 1.25%,including scutellarin,apigenin, luteolin, etc. and their glycosides; extraction solvent – 20% ethanol (Wightman et al., 2018;Heiner et al., 2018;Feistel etal., 2018).

Posology

Adultsandelderly

*Therapeuticindications1and 2:*Traditionalherbalmedicinalproductusedforthereliefofcoughassociatedwiththecommoncoldandfortherelief ofmildgastrointestinaldiscomfort (EMA/HMPC/39453/2015).
Singledose: 2-4 gofthecomminutedherbalsubstance in150-200mlof boilingwater asaherbalinfusion.
*Dailydose:*upto12gdailyforoneweek(EMA/HMPC/39453/2015).
Theuseinchildrenandadolescentsunder18isnotrecommended(EMA/HMPC/39453/2015).

*Therapeuticindication3:*Herbalmedicinalproductusedforstress-inducedimpairmentofcognitivefunction,memory, and mood(Behrendt etal., 2016;Dimpfel,2016a; Wightmanetal.,2018).
Single dose: 330 - 500 mg of the dried herbal extract (extraction solvent – 20 % ethanol, DER 5–9:1,containing0.5–1.5% flavonoids 0.1–0.4% caffeoylquinic acids) in capsule or tablet dosage forms.*Daily dose:* 660-1000 mg (in 2 capsule or tablet dosage forms) (Behrendt et al., 2016; Dimpfel, 2016a;Wightmanetal.,2018).TherapeuticIndication3isnot yetbeenassessedandapprovedyetbydrugauthorities(EMA/HMPC/201708/2022).

Durationofuse

Therapeutic indication 1: Traditional herbal medicinal product used to relieve cough associated with cold.Duration of treatment – 7 days. If the symptoms persist for longer than one week during the treatment, adoctorora qualified health care practitioner shouldbeconsulted. (EMA/HMPC/39453/2015).
Therapeutic indication 2: Traditional herbal medicinal product used to relieve mild gastrointestinaldiscomfort. Duration of treatment – 14 days. If the symptoms persist longer than two weeks during thetreatment, a doctor or a qualified health care practitioner should be consulted (EMA/HMPC/39453/2015).*Therapeutic indication 3:* Herbal medicinal product used for stress-induced impairment of cognitivefunction,memory, and mood. The duration of treatment is 4 - 6 weeks (Behrendt et al., 2016; Dimpfel,2016a; Wightman et al., 2018).

Methodofadministration

Oraluse(EMA/HMPC/39453/2015;Behrendtetal.,2016;Dimpfel,2016a;Wightmanetal.,2018).

Discussions,Limitations,andPerspectives

Recent extensive research on GMT suggests that GMT can be characterized as a putative adaptogendespite the fact that the mechanisms of action of GMT preparations have not been sufficiently studied indetail.
Whatisevidentinthissuggestion?

1. GMThasanexcellentsafetyprofilethatisinlinewith theearlierdefinitionofadaptogens(Wagner etal.1993):
    - anadaptogenmustbeinnocuousand mustnotinfluencenormalbodyfunctionsmorethanrequired.
    - anadaptogenmusthaveanormalizinginfluenceindependentofthenatureofthepathol ogicalstate;
    - anadaptogenmustshowanon-specificactivity,i.anincreaseinpowerofresistanceagainstphysical, chemicalor biologicalnoxiousagents,

2. Adaptogens are also known to exhibit numerous pharmacological effects associated with stress-system (neuroendocrine-immune complex) and have many indications for use in stress andaging-related disorders (Panossian &Efferth, 2022; Panossian et al, 2021; Panossian, 2017),including infectious diseases (Panossian and Brendler, 2020), gastrointestinal diseases (Panossianet al. 2020). GMT extracts and some purified compounds isolated from *Sideritisscardica*exhibitedpleiotropic activity, including cognitive improvement, stress-protective, neuroprotective,anxiolytic, anti-aging, anti-inflammatory, antimicrobial, gastroprotective, glycemic, anti-obesity,antioxidant, and anti-tumor activity. According to Hans Selye (1936), general adaptationsyndrometostressincludesanonspecificreaction, includingstomachulceration,thymus atrophy, adrenal hyperplasia, increased secretion of cortisol and catecholamines, etc.(Panossian etal2020).
3. Adaptogens have mild stress mimetic effects in the normal homeostatic range to increase theresilience of organisms and alleviate stress (Panossian et al, 2020; Anghelescu et al. 2018; Xia etal., 2016). GMT significantly increased cognitive functions and cerebral blood circulationparameters after a single administration of GMT in elderly adults but did not further improvecerebral blood oxygenation after repeated administration for 4 weeks, decreasing the state ofanxiety and improving cognitive function, unlike Gingko, suggesting that restored homeostasis(Wightmanet al., 2018).
4. The chemical composition of *Sideritisscardica*is characterized by a high content of compoundscontaining four common types of structural fragments (pharmacophores), including phenethan,phenylpropanoid,flavonon and steroid-like tetracyclic skeleton, including phenylethyl-phenylpropanoid glycoside acteoside (AC, *syn.* Verbascoside, 5). These pharmacophores arecovalently incorporated into the chemical structures of some active principles of adaptogenicplants, such as salidroside (**18**) rosavin (**19)** in *Rhodiola rosea* (Panossian et al., 2010; Bernatonieneet al.2023), eleuteroside B (**20**) in *Eleutherococcussenticosus*(Jia et al., 2021; Radix Eleutherococci,WHO monograph, 2002) which are structurally similar to catecholamines dopamine (**21)**,noradrenaline (**22)** and serotonin (**23)**, suggesting that they compete for receptors sites of proteinsinvolved in signalingpathwaysandcellular responses.

Chemicalstructures18-23here.

5. Acteoside (AC), found in a variety of plants, has pharmacologically useful actions for humanhealth, including depression, neuroprotection, cardiovascular protection, hepatoprotection, boneand cartilage protection in addition to wound-healing, antibacterial, anti-fungal,anti-leishmanial, hypoglycemic, antihypertensive, anti-epileptic, anti-inflammatory, and antitumoractivity in many experimental models through oxidative stress, apoptosis, anti-angiogenesis,anti-invasion, anti-metastasis, and anti-proliferative effects, and synergism with othercompounds through modulation of several pathways (Alipieva et al.,2014;Khan et al.,2022; Xiaoetal.,2022;Zhaoet al. 2023).
6. The health-promoting features of AC are likely due to involvement in many adaptive canonicalsignalingpathways,suchasMAPK,NF-κB,PI3K/AKT,TGFβ/Smad,andAMPK/mTOR(Xiaoetal., 2022).
7. A recent systematic review summarising the studies of pharmacological mechanisms ofantidepressantactivityofactoesinuncoveredthevariouspharmacologicalmechanismsincluding (i) - modulation of monoamine neurotransmission, (ii) - inhibition of the hyperactivity ofhypothalamic-pituitary-adrenal (HPA) axis, (iii) - promoting of neuroprotection by inhibitingapoptosis,inhibitingERstress,maintainingCa2+homeostasis,up-regulatingautophagy,and

(iv)–suppressionofoxidativestressandactivationof innateantioxidantdefensesystem(Zhaoet all.,2023).

ItshouldbeemphasizedthatGMTextracts,likeanyherbalextract,consistofmanychemicalcompoundsthat interact both in a synergistic and antagonistic manner, suggesting that the effects of purifiedcompounds cannot be simply extrapolated and mechanistically included in network analysis *in silico*without validation in experimental studies of gene expression, pharmacological and clinical studies(Panossian,2023;Panossian andEfferth, 2022;Panossianetal., 2015;Panossianetal., 2013)

Further research is necessary to ensure GMT compliance with the recent definition of adaptogens(Panossian et al. 2020) as "*plant extract that increases adaptability, resilience, and survival of organisms tostress" with "multitargeteffectsonneuroendocrine-immune systemincluding:*

(i) triggeringintracellularandextracellularadaptivesignaling pathwaysthatpromotecellsurvivalandorganismalresilience in stress(Panossianet al.2018),

(ii) regulation of metabolism and homeostasis via effects on expression of stress hormones (corticotropinandgonadotropin-releasinghormones,urocortin,cortisol,neuropeptideY,heatshockprotein sHsp70)and their receptors"(Panossianet al. 2018),and

"indicated for use in stress-induced fatigue, mental and behavioral disorders, aging-associated diseases" (Panossian,2017; Panossian,2013).

The recent findings supported by preclinical and clinical data suggest using *Sideritisscardica*extracts toimprovecognitivefunctionsandreducetheriskofage-relatedcognitivedeclineandneurodegenerativedisorders.

Further clinical trials and some pharmacognostic characteristics are worthy of implementing nationalmonographsonHerbaSideritis.

Conclusions

Greek Mountain Tea has been used for millennia. Current human trials confirm that GMT, administeredat the rate of 950 mg/day for 28 days, acts as a triple monoamine transmitter reuptake inhibitor,increasing blood flow to the brain, especially to the prefrontal cortex, and improving the flow of oxygento all body tissues, including to the brain. GMT slows and reverses the formation of beta-amyloid plaque,improves overall cognitive performance, improves the ability to remain focused and access workingmemory, improves reaction time, reduces anxiety, and improves mood. These major findings from acollaboration of British and German researchers concluded that polyphenols ferulic, chlorogenic acid andflavonoid apigenin are the likely cause of these benefits. A German review of more than 4,000 studies onhealthyelderlyhumansubjectsconcludedthatspecificpolyphenols,includingthosefoundinGMT,crossthe blood-brain barrier, significantly improving information processing speed, executive function, andneuron function while reducing inflammation and free radical oxygen damage in the brain. In addition, ajoint German-Norwegian study published in 2016 confirmed that highly enhanced cognitive function inelderlylabanimals given GMTconcludesit"mightbea potent,well-tolerated optionfortreating symptomsofcognitiveimpairmentintheelderly…""Well-tolerated"isacrucialconcepthere.Nosevereside effects have been attributable to the use of GMT, even long-term use, as is common among ruralpeopleinGreece and surroundingcountries.

A part of this monograph has focused on GMT's adaptogenic activity, which is a multitasker thatprovidesthebodywithwhatitneedstoincreaseresistance,resilience,andsurvivalplayingasimilarrolein defending the plant against environmental challenges, including viruses, harmful bacteria, insect-borne diseases, excessive UV rays, environmental challenges, and the physiological ravages of chronicstress.

Thismonographprovidesextensiveknowledge andessentialreferencesforassessmentsofHerbaSideritispreparations' safety, efficacy, and quality to support drug regulatory bodies developing international orregional monographs on medicinal plants or national formularies on evidence-based and traditionalherbal medicines. It includes details of botanical descriptions, chemical constituents, dosagerecommendations, adverse effects, and interactions for health professionals, researchers, andpolicymakers, aiding in evidence-based practices and ensuring the safe use of medicinal products. Thismonograph is intended primarily to promote harmonization in the use of herbal medicines with respectto levels of safety, efficacy, and quality control; it is not intended to replace official compendia such aspharmacopeias,formularies, or legislative documents.

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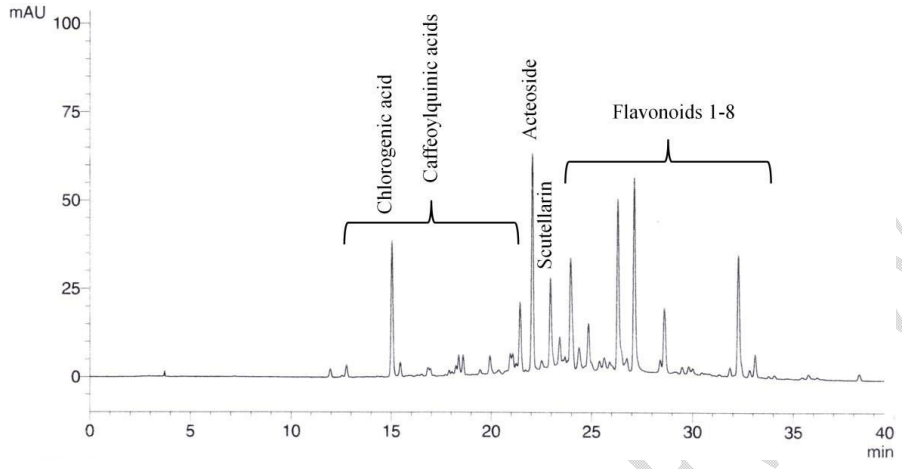


Figure1: TypicalHPLCfingerprintof20%ethanolic*S.scardica*extract(DERnative:7.2:1);thecontentofquality markers acteoside,caffeoylquinic acids,and flavonoids was quantified by UV detection at 330nmaccordingtotheFinzelbergGmbH& Co.KGmethod(Heineretal.,2018; Feisteletal., 2018).

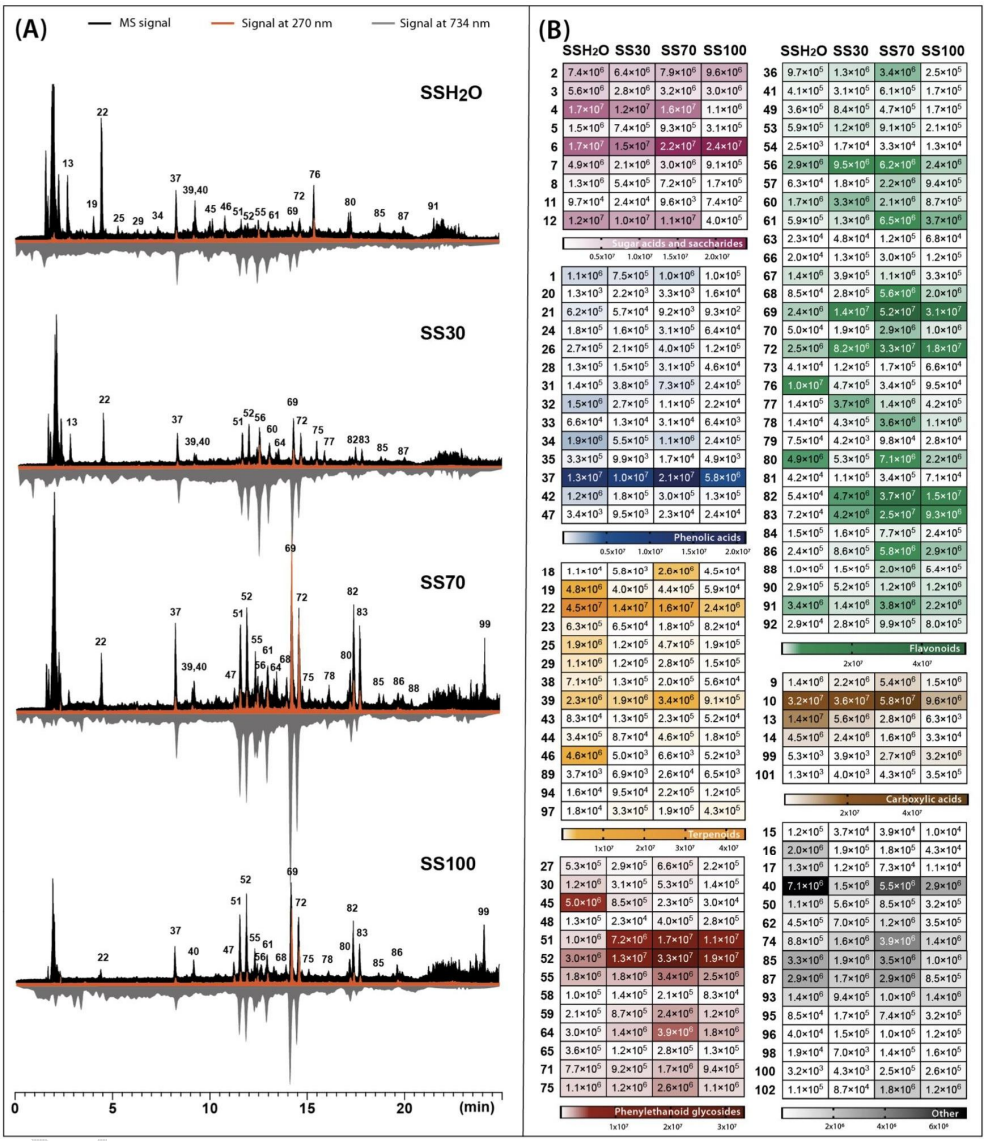
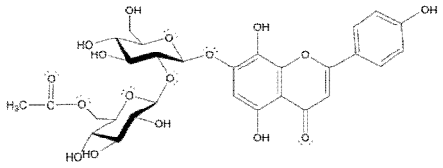


Figure 2. HPLC fingerprint of *Sideritisscardica*70% ethanolic extracts (Mroz et al. 2023). The content(w/w), of primary principal components analysis in the extract (Petreska et al., 2011) corresponding topeaks**51** ofLavandulifoliside***(8)*-**1.26± 0.65%,**52**–Acteosid/Verbascoside***(5)*-**1.8 ±0.0.45%;**69**-Iso-scutellarein7-O-[6’’’-O-acetyl]-allosyl(1→2)-glucoside***(1)* -**0.6±0.25%);**and72**-4’-O-Methylhypolaetin 7-O-[6’’’-O-acetyl]-allosyl(1→2)-glucoside***(3)***-0.84±0.21%

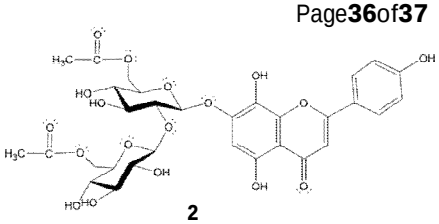
Table1.Theriskbias,reporting,andqualityscoresoftwoavailablerandomizedplacebo-controlledtrialsassessed by Cochrane (Higgins et al., 2011), Jadad (Jadad et al., 1996), and CONSORT (Gagnier et al.,2006)criteria.

Study author	Random sequencegenerati on	Allocationco ncealment	Blinding ofparticipants andpersonnel	Blinding ofoutcome assessment	Incompleteo utcomedata	Selectivereporting	Other biases(industry funding,conflicts ofinterest, etc.).	Jadad's Qualityscore	Interventions reporting
Dimpfel et al.,2016b	?	?	?	?	⊕	⊕	⊖	1	?
Wightman etal.,2018	⊕	?	⊕	?	⊕	⊕	⊖	4	⊕ ?

Lowrisk ofbias ⊕ Highrisk ofbias ⊖ Unclearriskofbias ?



1



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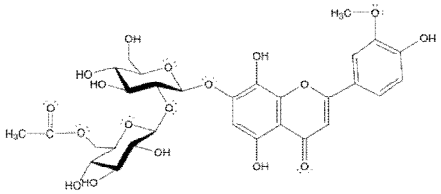

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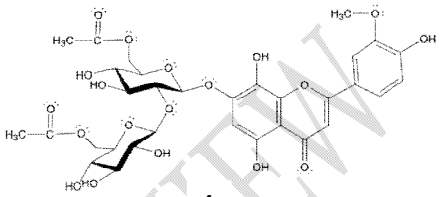

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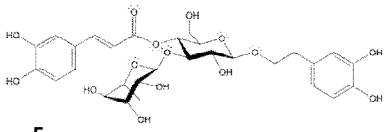

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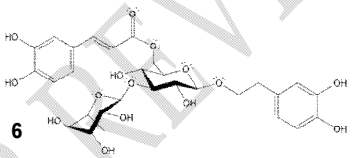

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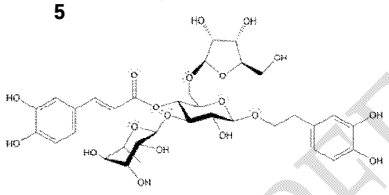

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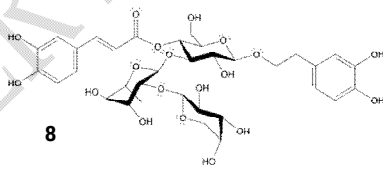

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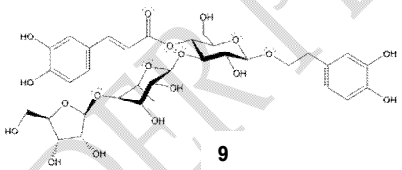

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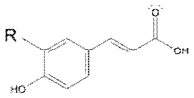

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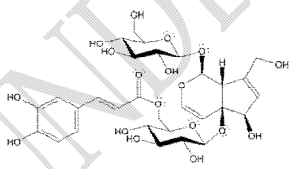

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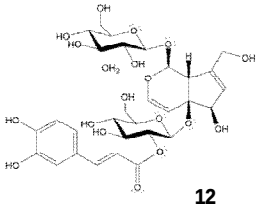

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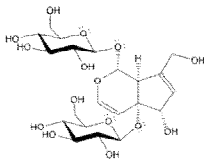

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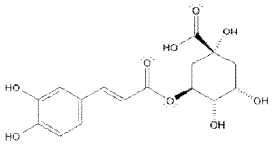

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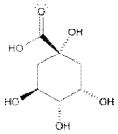

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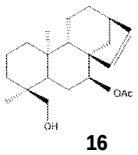

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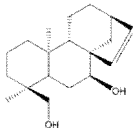

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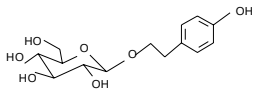

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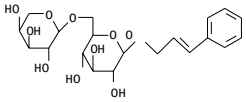

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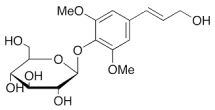

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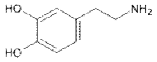

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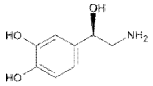

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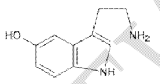

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