Herba Sideritis: Insights from a Herbal Monograph with Particular Reference to Adaptogenic Potential in Neurodegenerative Disorders and Aging-related Cognitive Decline

Edition 1

Alexander Panossian and Terrence Lemerond

BP International

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PREFACE

This chapter is based on the first herbal monograph on *Herba sideritis* L., Greek Mountain Tea, recent scientific publications, and our experience. Our main aim was to summarize the accumulated knowledge about this valuable medicinal plant and focus on its adaptogenic potential in neurodegenerative disorders and aging-related cognitive decline in a simplified way to make it easy to understand for anyone, regardless of educational background. That is a challenge due to the daunting complexity of living organisms and the lack of sufficient knowledge of the laws of life. However, we made a glimpse of simplicity lurking within this complexity. This chapter is apparently for advanced readers, despite the hope that it would be apparent to anyone with a curious and thoughtful mind.

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ABSTRACT

Background: Greek mountain tea (GMT), Herba Sideritis (*Sideritis scardica* Griseb.), is traditionally used to treat the common cold and mild gastrointestinal disorders. *Sideritis* spp. has been characterized as a genus with more than 150 perennial species widely distributed in the Mediterranean and the Canary and Madeira Islands. GMT was adopted in 2015 in the European Union as a traditional herbal medicine. Recent studies suggest its potential efficacy for reducing the risk of age-related cognitive decline and neurodegenerative diseases, which could be associated with the common mechanisms of action.
Aims and Hypothesis: The aims of this monograph were: (i) to systematically update new evidence of the quality, efficacy, and safety of GMT preparations and validate their potential health benefits, and (ii) to elaborate a rationale for a mode of polyvalent pharmacological action, which is likely associated with a regulation of the neuroendocrine-immune complex (stress system).
Methods: Literature screening using the Pubmed database and original publications were assessed according to WHO criteria for monographs of herbal medicines.
Results: *Sideritis scardica* extracts and its ingredient phenylethyl-phenylpropanoid glycoside acteoside (AC, *syn.* verbascoside) exhibited cognitive improvement, stress-protective, neuroprotective, neurogenesis, anxiolytic, anti-aging, anti-inflammatory, antimicrobial, gastroprotective, glycemic, anti-obesity, antioxidant, and anti-tumor activity. According to the findings, the combination of

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Sideritis scardica with vitamin B may be relevant for persons solving cognitive tasks under conflict and/or noise (e.g., open-plan offices or car-driving) and support that the tested product alleviates stress-induced impairment of executive functioning (working memory, cognitive flexibility, controlled behavioral inhibition). The recent findings supported by preclinical and clinical data suggest using Herba Sideritis extracts to improve cognitive functions and mental disorders in aging.

Conclusion: This monograph provides systematic information on the safety, efficacy, and quality of Herba Sideritis, paving the way for its potential use in reducing the risk of age-related cognitive decline and neurodegenerative disorders. It includes details of botanical descriptions, chemical constituents, dosage recommendations, adverse effects, and interactions for health professionals, researchers, and policymakers aiding in evidence-based practices and ensuring the safe use of medicinal products. Further preclinical and clinical research is crucial to fully validate GMT's health benefits and unravel the mechanisms underlying its adaptogenic effects.

Keywords: Herba Sideritis; Sideritis scardica; monograph; cognitive functions; herbal medicine; adaptogen; neuroprotective; inflammaging.

1. INTRODUCTION

Mount Olympus is the legendary home of the Greek gods. It's the mythological home of the most revered symbols of the ancient Greek religion and a physical symbol; it's one of Europe's highest peaks, soaring more than 9,500 feet above the serene Aegean Sea. The sacred mountain is high, dry chaparral with a wealth of biodiversity, the birthplace of one of the Greek Mountain Tea (Sideritis scardica: translation "he who is made of iron"), frequently called "Olympos" tea by Greeks and their Mediterranean neighbors. Also called "ironwort" or "shepherd's tea," Greek Mountain Tea (GMT) grows wild at altitudes above 3,200 feet. It's a survivor, growing wild and thriving on poor soil and limited water. Most Greek Mountain Tea is wild-grown, harvested by local farmers, and minimally processed at those same high altitudes. Its popularity is well-deserved.

In ancient times, Greek shepherds began to harvest GMT to help them stay healthy, warm, and mentally alert. The medicinal use of Greek mountain tea (GMT) was described by the Greek physician Dioscorides in De Materia Medica in 77 C.E. Hippocrates, the father 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 has been widely acclaimed for its vast healing power. Modern scientific research confirms GMT can combat Alzheimer's disease, lower blood pressure, reduce the risk of heart attacks and strokes, improve digestive health, increase bone density, enhance immune function and prevent colds and flu, reduce anxiety and depression, reduce insulin resistance, promote weight loss, relieve joint pain. The most exciting for us is GMT's effectiveness against Alzheimer's disease and dementia, confirmed through several well-researched

published studies. All these benefits sound like a recipe for a healthy, long life, especially for older adults. This is the subject of this book chapter so these findings will be addressed in detail (Lemerond, 2023).

GMT was adopted in 2015 in the European Union as traditional herbal medicine, Herba Sideritis (*Sideritis scardica* Griseb.), for treating the common cold and mild gastrointestinal disorders; however, no registered or authorized well-established medicinal products in the EU / EEA Member States (EMA/HMPC/39455/2015). Since then, considerable studies have been conducted suggesting that GMT can 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; Tumou et al., 2023).

The recent findings supported by preclinical and clinical data suggest using Herba Sideritis extracts to improve cognitive functions and mental disorders in aging. Furthermore, recent publications show *Sideritis scardica* extracts and some purified compounds exhibited cognitive improvement, stress-protective, neuroprotective, anxiolytic, anti-aging, anti-inflammatory, antimicrobial, gastroprotective, glycemic, anti-obesity, antioxidant, and anti-tumor activity. Such pleiotropic effects of GMT on the neuroendocrine-immune complex (stress system) are typical of adaptogenic activity (Wagner et al., 1993; Panossian & Efferth, 2022; Panossian et al. 2021; Panossian and Brendler, 2020; Panossian, 2017; Panossian, 2023).

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

2. HERBAL NAME

Sideritis scardica Griseb. (order *Lamiales*, family *Lamiaceae*, genus *Sideritis*) is an Internationally accepted name (WFO PlantList, 2023) for Herba Sideritis. The Latin name Sideritis L. derives from the Greek word (Panossian, 2023) "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, dried flowering tops or aerial parts collected during the flowering season.

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; Panossian, 2023), including:

- Ελ
- ληνικό Τσάι του βουνού / Greek mountain tea, 'Olympus tea' (Greece),
- Caj Mali (Albania),
- Mursalski Tee, Pirinski Tee or 'Alibotushkitea' (Bulgaria),
- Планински чај /Planinski Tea, 'Sharpla-ninsi chaj' (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),
- Երնջա / Ernja (Armenian).

3. 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). *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 a special regime for conservation and use due to its intensive collection for years (Todorova et al., 2014; Panossian, 2023).

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).

4. PLANT MATERIAL OF INTEREST: DRIED AERIAL PARTS

General appearance: 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 oblanceolate (long lanceolate) to obtuse - in the lowest veins; to longer in the middle veins; to lanceolate (linear-lanceolate) - acute in the highest veins. Lower leaves have a short stalk, 40-80 mm long, 6-20 mm wide. Upper leaves from the 4th vein upward are prostrate as the stem is shortened gradually from lower to upper 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 a lemon-yellow color. 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; the receptacle is tube cup-shaped, with ten veins and five equal teeth, pubescent and coated by fine intertwined hairs. The whorl is yellow with a tube hidden in the receptacle, two-lipped with a three-lobe lower lip. Four stems are hidden in the tubes of the whorl.
- The fruit is dry and decomposed into four nuts. Leaves and stems are white, woolly-villous (Heywood, 1972; Yaneva & Balabanski, 2013; Panossian, 2023)

Depending on the sea level and climate properties, the plant comes out in blossom from the end of June to the beginning of September. (Heywood, 1972). GMT is one of the medicinal and aromatic plants with great global economic importance due to its nutritional value, pharmacological activities, and potential applications in the cosmetic and perfume industries (Kaparakou et al., 2023).

Organoleptic properties: Its smell is pleasant, and the taste is slightly bitter (Heywood, 1972). GMT infusions have a pleasant characteristic aroma (Chrysargyris et al., 2023).

General identity tests: Macroscopic examinations (Heywood, 1972), thin-layer chromatography (Heiner et al., 2018; Feistel et al., 2018; Pihan et al., 2021), and HPLC (Mroz et al., 2023; Heiner et al., 2018; Feistel et al., 2018).

Purity tests:

Microbiological: Tests for specific microorganisms and microbial contamination limits were described in the WHO guidelines on assessing the Quality of herbal medicines with reference to microbiological contaminants (Quality Control Methods for Medicinal Plant Materials, 1998).

Foreign organic matter: *Aerial part:* not more than 2% as described in the WHO guidelines on assessing the Quality of herbal medicines with reference to foreign organic matter (Quality Control Methods for Medicinal Plant Materials, 1998).

Total ash: *Aerial part:* not more than 10% as described in the WHO guidelines on assessing the Quality of herbal medicines with reference to total ash (Quality control methods for medicinal plant materials, 1998; Panossian, 2023).

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

Water-soluble extractive: Aerial part: not less than 15.0% as described in the WHO guidelines on assessing the Quality of herbal medicines with reference to water-soluble extractives (Quality control methods for medicinal plant materials, 1998).

Loss on drying: Aerial part: not more than 12% w/w (Hofrichter et al., 2016); 5.5% w/w/ (Mroz et al., 2023).

Pesticide residues: The recommended maximum limits of pesticides (European Pharmacopeia, 2008) and the WHO guidelines on assessing the Quality of herbal medicines with reference to contaminants and pesticide residues (Quality control methods for medicinal plant materials, 1998).

Heavy metals: For maximum limits and analysis of heavy metals, consult the WHO guidelines on assessing the Quality of herbal medicines with reference to contaminants and residues (Quality control methods for medicinal plant materials, 1998; Panossian, 2023).

Radioactive residues: Where applicable, consult the WHO guidelines on assessing the Quality of herbal medicines with reference to contaminants and residues (Quality Control Methods for Medicinal Plant Materials, 1998).

5. CHEMICAL ASSAYS

Total polyphenolics**:** not less than 5.82–15.0% (mean content 8.6 ± 2.6%) (Petreska et al., 2011); 5.4 ± 0.2% (Grozdanova et al., 2020), 10.1% ± 0.1% (Lazarova et al., 2023), 13.5% (Danesi et al. 2012). Alternatively, the total polyphenols content was determined using Folin-Ciocalteu's reagent and gallic acid as a calibration standard; the results were expressed in mg gallic acid equivalents per 100 g dry weight (Lazarova et al., 2023; Panossian, 2023).

Major principal components analysis:

- 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%- in dried water- ethanolic extracts (Heiner et al., 2018; Feistel et al., 2018); 151.54 ± 10.86 mg/g of dry

extract (15.1% of dry extract, DER 8:1, 1.9% of herbal substance (Zheleva-Dimitrova et al., 2024),

- Lavandulifoliside **(8)**: not less than 0.67–2.61% (mean content 1.26 ± 0.65%),
- Iso-scutellarein 7-O-[6'''-O-acetyl]-allosyl(1→2)-glucoside, **(1):** not less than 0.3–1.1% (mean content 0.6 ± 0.25%), 107.44 ± 9.07mg/g of dry extract (15.1% of dry extract, DER 8:1, 1.9% of herbal substance (Zheleva-Dimitrova et al., 2024),
- 4'-O-Methyl-hypolaetin 7-O-[6''' -O-acetyl]-allosyl(1→2)-glucoside **(3):** not less than 0.56–1.23% (mean content 0.84 ± 0.21%) (Petreska et al., 2011), 78.33 ± 3.29 mg/g of dry extract (7.8% of dry extract, DER 8:1, 1.0% of herbal substance (Zheleva-Dimitrova et al., 2024),
- 4 ′ -O-Methyl-iso-scutellarein-7-O[6 ‴ -O-acetyl]hexosyl-(1 → 2)-hexoside: not less than 107.44 ± 9.07 mg/g of dry extract (10.7% of dry extract, DER 8:1, 1.3% of herbal substance (Zheleva-Dimitrova et al., 2024).

Total phenylpropanoids**:** not less than 2.88–9.68% (mean content 5.1 ± 1.95%) (Petreska et al., 2011a) analyzed by liquid chromatography-diode array detector – electrospray using high-performance liquid chromatography coupled to UV-Vis diode array detection and tandem mass spectrometry with an electrospray ionization source (LC/DAD/ESI-MS) (Petreska et al., 2011a) and high-resolution mass spectrometry HR-LC-ESI-Orbitrap-MS/MS analysis in negative ion mode (Mroz et al., 2023; Panossian, 2023).

Hydroxycinnamic derivatives: not less than 0.08–0.58% (mean content 0.22 ± 0.15%) (Petreska et al., 2011). Hydroxycinnamic acids were quantified using 5-caffeoylquinic acid as external standard at 330 nm; identification of hydroxycinnamic acid derivatives containing caffeic, ferulic, and coumaric acid moieties was conducted by UV detection of two peaks detected by absorption bands at 320-325 nm and 242 nm and by a sharp diagnostic shoulder at 290-300 nm that typical of compounds containing a hydroxycinnamic group (Petreska et 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 as verbascoside equivalents at 330 nm; Identification of phenylethanoid containing phenylpropanoids was by absorption peaks at 232, 246, 288 and 332 nm and fragmentation patterns characteristic of phenylethanoid glycosides acylated with caffeic and ferulic acid, thus allowing their identification as glycosyl hydroxycinnamic acids (Petreska et al., 2011; Panossian, 2023).

The content of phenylethanoid glycosides ranged from 0.074 – 15.15% in dry water extract (lyophilized infusion, DER 8:1), 0.01- 1.9% of herbal substance (Zheleva-Dimitrova et al., 2024); caffeic acid oligomers -in the rage 0.02 - 0.6 %, caffeoylhexaric acids ranged from 0.08 - 0.35% in dry water extract (lyophilized infusion, DER 8:1) (Zheleva-Dimitrova et al., 2024).

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 isoscutellarein glucosides were quantified and expressed as isoscutellarein 7-O-[6‴-O-acetyl]-allosyl (1→2)glucoside equivalents at 300 nm. Alternatively, the total flavonoid content was determined using AlCl3 reagent and expressed as mg quercetin equivalents per 100 g dry weight (Lazarova et al., 2023).

Total flavones**:** not less than 0.20- 0.50 ± 0.02% (Janeska et al., 2007).

Flavonoid-7-O-diglycosides: not less than 0.05–0.52% (mean content 0.24 ± 0.15%) (Petreska et al., 2011).

Flavonoid acetyl glycosides*:* not less than 2.5–5.13% (mean content 3.3 ± 0.8%) (Petreska et al., 2011).

Diterpenes *(Siderol and sideridiol):* 0.13-1.8% (Ibraliu et al., 2014).

Essential oil: not less than 0.03% (% volume per weight of herb, v/w) of etheric oil determined by steam 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%) and geraniol (5.6%) (Bojovic et al., 2011; Tadić, Bojović, et al. 2012a; Kaparakou et al., 2023; Panossian, 2023).

6. MAJOR CHEMICAL CONSTITUENTS

Over 200 plants' secondary metabolites have been identified in the aerial part of *Sideritis scardica,* 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; Ibraliu et 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; Kaparakou et al., 2024; Papanikolaou et al.,2024; Segneanu et al.,2024; Zheleva-Dimitrova et al., 2024). 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, it was identified in that study (Denessi et al.,2013) and other phytochemical studies of Sideritis extracts, which are known free of caffeine (Zyzelewicz et al., 2020; Walbroel, and Feiste, 2010; Panossian, 2023).

Sideritis scardia is a rich source of polyphenols with a content range from 5.8% to 15.0% of dry plant material. The largest portion of polyphenols consists of **phenylpropanoids** (caffeoyl-, feruloyl-, and coumaroyl-esters) derivatives (2.88–9.68%), containing phenylethanoid-glycosides moiety (2.8–9.1%, including Acetoside, Allysonoside, Echinacoside, Forsythoside A, Lavandulifolioside, Leucoseptoside A, Martynoside, Verbascoside, Isoverbascoside, Samioside), *monoterpenoids (*iridoids*) (*Stachysosides E **(10),** Stachysosides G, 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**, containing hypocretin and iso-scutellarein aromatic cores in their structure (2.55–5.65%).

Among 102 compounds identified in 70% ethanolic extracts of *Sideritis scardica* areal parts (Mroz et al., 2023), the main major active constituents included:

- ***flavone 7-0-glycosides*** Iso-scutellarein 7-O-[6’’’-O-acetyl]-allosyl(1→2)-glucoside **(1),** Iso-scutellarein 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);**
- ***phenylethyl-phenylpropanoids glycosides*** acteoside/verbascoside **(5),** Iso-acteoside **(6),** Forsythoside B **(7)**, Lavandulifolioside **(8)**, Samioside **(9)** and ***phenylpropanois*** **(10)**
- ***monoterpenoid (*iridoids*) phenylpropanoids glycosides*** Stachysosides E **(11),** Stachysosides G **(12**), Melittoside (**13**) , Chlorogenic acid **(14),** and D-(−)-Quinic acid **(15);**
- ***Diterpenes*** Siderol (**16)** and sideridol (**17**).

Chemical structures 1-17 here.

Differential analysis of *Sideritis scardica* and *Sideritis raeseri* of 70% ethanolic extracts proved that substance 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 the distinction between these varieties including two prominent 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's was the major in *S. raeseri* extract (Mroz et al., 2023; Panossian, 2023).

A decrease in the polarity of extraction solvent (from 0% to 30%, 70%, to 100% ethanol in water) increases the content of phenolic compounds. It significantly affects the HPLC profile of *Sideritis scardica* extracts, Fig. 1 (Panossian, 2023).

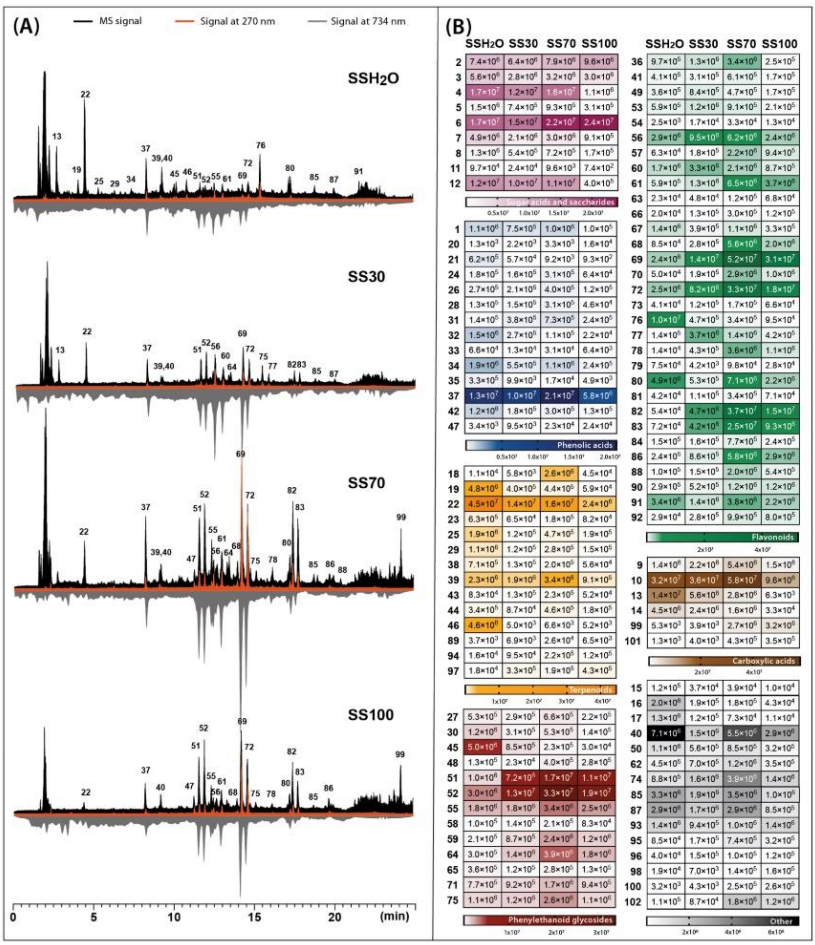


Fig. 1. A - LC-Q-Orbitrap fingerprint of *Sideritis scardica* extracts: water extract SSH_2O; 30% ethanol SS30; 70% ethanol extract SS70; ethanol extract SS100. The total ion chromatograms detected in negative mode (black) combined with chromatograms registered by UV-Vis detector at 270 nm (orange) and antioxidant profiles registered at 734 nm after post-column derivatization with ABTS (grey). B – shows heat maps representing the mean MS peak area value of the identified compounds (Mroz et al. 2023). The content (w/w), of primary principal components analysis in 70% of the extract (Petreska et al., 2011) corresponding to peaks 51 of Lavandulifoliside *(8)* - 1.26 ± 0.65%, 52 – Acteosid / Verbascoside *(5)* - 1.8 ± 0.0.45%; 69 - Iso-scutellarein 7-O-[6'''-O-acetyl]-allosyl(1→2)-glucoside *(1)* - 0.6 ± 0.25%); and 72 - 4'-O-Methylhypolaetin 7-O-[6''' -O-acetyl]-allosyl(1→2)-glucoside *(3)* - 0.84 ± 0.21%

Infusion of areal parts of *Sideritis scardica* in boiled water significantly increases the yield of polyphenols (Papanikolaou et al., 2024; Zheleva-Dimitrova et al., 2024). A typical HPLC fingerprint of *Sideritis scardica* water extract (lyophilized infusion areal parts) is shown in Fig. 2, where 103 components were identified (Zheleva-Dimitrova et al., 2024), including acteoside/verbascoside (**5**) 15.1% of dry extract – 1.9% of herbal substance, and flavones 7-0-glycosides isoscutellarein-7-O-hexosyl-(1 → 2)-[6 ″ O-acetyl]-hexoside **(1),** and 4 ′ -O-methyl-iso-scutellarein-7-O[6 ‴ -O-acetyl]hexosyl-(1 → 2)hexoside as a major peaks.

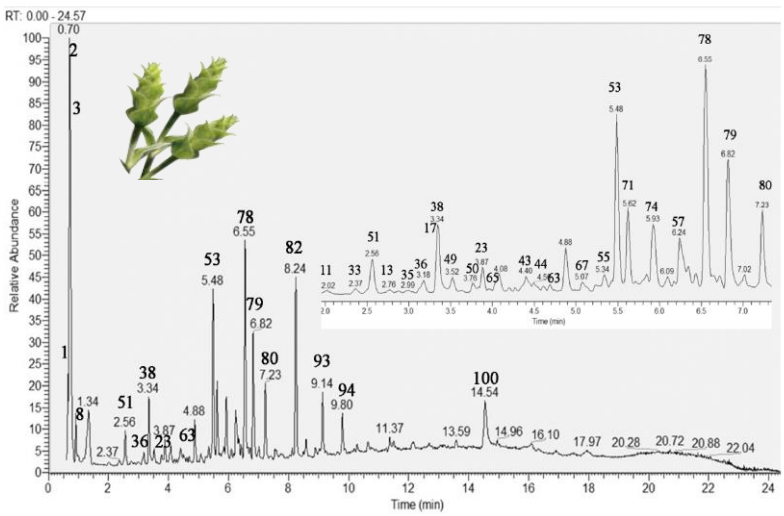


Fig. 2. Total ion chromatogram (TIC in negative ion) UHPLC-HRMS of *S. scardica* water extract (DER native: 8:1, yielded.12.5%) - infusion in boiled water (1:20 w/v) and extracted for 15 min at room temperature). Major peaks are numerically labeled per original publication (Zheleva-Dimitrova et al., 2024) and identified as follows:

- *Peak 38 - 4-caffeoylquinic acid, 7.65 ± 0.96, mg/g = 0.76% of dry extract,*
- *Peak 51 – decaffeoyl aceteoside/verbasoside, 35.09 ± 2.46, mg/g = 3.5% of dry extract,*
- *Peak 53 - acteoside/verbasoside (5), 151.54 ± 10.86 mg/g = 15.1% of dry extract – 1.9% of herbal substance,*
- *Peak 57 - phenylethanoid glycosides leucoseptoside A, 22.80 ± 0.82, mg/g = 2.3% of dry extract,*
- *Peak 71 - isoscutellarein 7-O-hexosyl (1 → 2)-hexoside, 47.47 ± 0.9, mg/g = 4.7% of dry extract,*
- *Peak 74 – methylhypolaetin 7-O-dihexoside, 17.33 ± 0.25, mg/g = 1.7% of dry extract,*
- *Peak 78 - isoscutellarein-7-O-hexosyl-(1 → 2)-[6 "O-acetyl]-hexoside (1), 151.70 ± 14.79, mg/g = 15.2% of dry extract,*
- *Peak 79 - 4′ -O-methylhypolaetin-7-O-acetyl‑hexosyl‑hexoside (3), 78.33 ± 3.29, mg/g = 7.8% of dry extract*

- *Peak 80 - 4′ -O-methylisoscutellarein 7-O-dihexoside, 24.20 ± 0.98, mg/g = 2.4% of dry extract,*
- *Peak 82 - 4 ′ -O-methylisoscutellarein-7-O[6 ′ ′ ′ -O-acetyl]hexosyl-(1 → 2)hexoside. 107.44 ± 9.07, mg/g = 10.1% of dry extract.*

A representative UPLC-ESD-HRMS chromatogram of SidTea+™ extract of *S. scardica* water extract obtained at 85◦C for 3 h used as a lyophilized powder in capsules form (Fig. 3) was recently used in phase 1 study in 14 healthy subjects (Papanikolaou et al., 2024; Panossian, 2023).

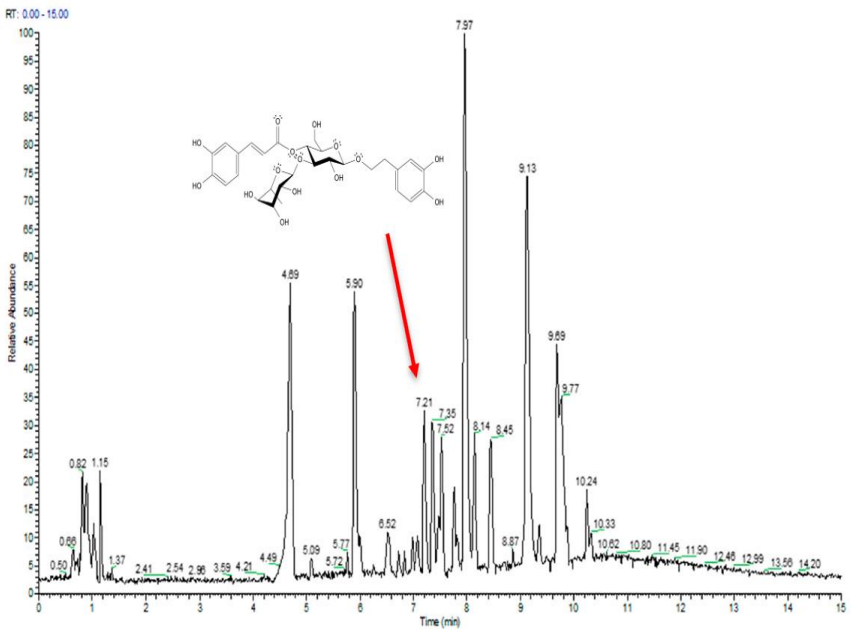


Fig. 3. Typical UPLC-ESD-HRMS chromatogram of SidTea+™ extract of *S. scardica* water extract; peak of acteoside/verbasoside (5) at RT 7.21 (Papanikolaou et al., 2024).

The content of acteoside (*syn.* verbascoside) was highest in 20% EtOH (v/v) *S. scardica* extract containing 6.25% total polyphenols, including flavonoids (1.18%) and caffeoylquinic acids (0.41%) compared with *S. scardica* extracts used water, 50% ethanol and heptane as extraction solvents (Heiner et al., 2018; Feistel et al., 2018), Fig. 4 (Panossian, 2023).

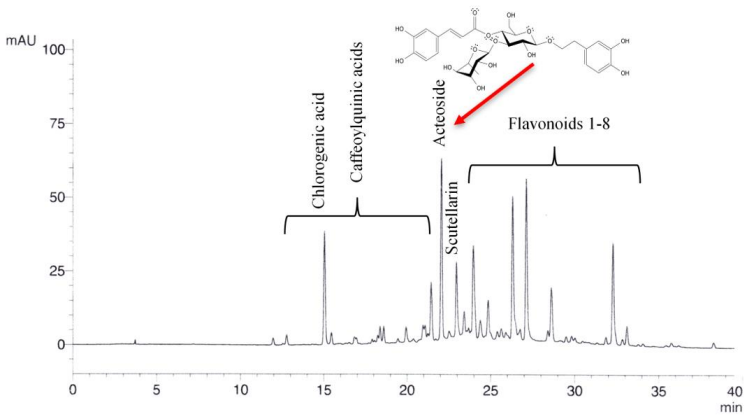


Fig. 4. Typical HPLC fingerprint of 20% ethanolic *S. scardica* extract (DER native: 7.2:1); the content of quality markers acteoside, caffeoylquinic acids, and flavonoids was quantified by UV detection at 330 nm according to the Finzelberg GmbH & Co. KG method (Heiner et al., 2018; Feistel et al., 2018)

Acteoside is presumably the most suitable quality control active marker, Fig. 4, for drug development (Heiner et al., 2018; Feistel et al., 2018) in clinical studies (Wightman et al., 2018; Dimpfel et al., 2016b), due to its known neuroprotective, anti-inflammatory, antibacterial and antileishmanial activity (Moussavi et al., 2022). Acteoside was pharmacologically active *in vitro* and *in vivo* models of neurodegenerative, behavioral, and other stress and stress-induces disorders (Alipieva et al.,2014; Khan et al.,2022; Xiao et al., 2022; Zhao et al., 2023), suggesting that they can be used as active markers of quality of standardized or quantitative extracts of Active Pharmaceutical Ingredient to ensure of reproducible efficacy of GMT medical products (Heiner et al., 2018; Feistel et al., 2018; Panossian, 2023).

However, further studies are needed to demonstrate the additive, potentiating, or synergistic effects and lack of antagonistic interaction of other GMT ingredients, including their dose-response and pharmacokinetic studies in matching doses to GMT. Thus, synergistic effects between acteoside, chlorogenic acid, and flavonoids might plausibly play a role in the health-beneficial and nootropic profile of *S. scardica*, particularly in Alzheimer's Disease (Moussavi et al., 2022).

The chemical structure of Acteoside/Verbascoside includes dihydroxyphenyl-propenyl (C6–C3) and dihydroxyphenyl-ethyl (C6–C2) pharmacophores covalently bound to sugar moieties. It is widely spread in the plant kingdom; it occurs in numerous species in all the families of *Lamiales* and many families of *Asterales*, *Cucurbitales*, and *Mangoliales* orders (Alipieva et al., 2014). They have different chemical compositions, pharmacological signatures, and profiles

compared to GMP, which differs from any purified active constituent. In this context, an assertion that acteoside is the only compound "responsible" for the activity of GMT is likely unjustified (Panossian, 2023).

Twenty minerals in over-ground parts of the plant and in water tea infusions were determined. As most affluent, 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 the 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).

7. MEDICINAL USES

Uses supported by clinical data: Mental enhancement and improvements in cognitive performance (Behrendt et al., 2016; Dimpfel, 2016a; Dimpfel, 2016b; Wightman et al., 2018***)***

Uses described in pharmacopeias and well-established documents: An ancient Pharmacopoeia of medicinal plants and medicines dated 1st BC describes the use of Herba Sideritis wet packs or compresses in wound healing (Dioscorides s, De Materia Medica IV, 37). There is no existing monograph in National Pharmacopoeias or National Codexes currently used in the Member States or any other monograph on *Sideritis herba*. There are no registered or authorized well-established medicinal products in the EU / EEA Member States (EMA/HMPC/39455/2015) (Panossian, 2023).

Uses described in traditional medicine: Greek mountain tea was traditionally used as an 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 the body of poisons (Gonzales-Burgos et al., 2011; Todorova et al., 2014; Tsioutsiou et al., 2019).

According to the EMA Assessment Report on *Sideritis scardica* Griseb., 2016, mountain tea has been traditionally used to aid digestion, strengthen the immune system, and suppress the common cold, the flu. The evidence of traditional medicinal use of *Sideritis herba* is confirmed by a large number of publications providing consistent information *(*EMA/HMPC/39454/2015). The indications of *Sideritis herba* for the relief of cough associated with cold and mild gastrointestinal disorders were adopted for the 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 oral use (EMA/HMPC/39453/2015).

8. PHARMACOLOGY

8.1 Experimental Pharmacology – Preclinical *In vitro* and *vivo* Studies

Primary pharmacodynamics: Primarily, pharmacodynamics studies of *Sideritis scardica* water extract are related to the traditional use of common cold and mild gastrointestinal disorders, supported by the antibacterial and anti-inflammatory effects of *Sideritis scardica* water extract in experiments *in vitro* and *vivo.* Meanwhile, recent preclinical and clinical studies of *Sideritis scardica* alcoholic extracts suggest their potential use in the treatment of cognitive and mental disorders, which can be included in the main indication for evidence of the use of the new medicinal product (Panossian, 2023).

Cognitive functions, mental disorders, and neuroprotective activity: *Sideritis scardica* 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). In addition, *Sideritis scardica* extracts reduced amyloid-β aggregation and neurotoxicity in Alzheimer Disease mouse models, in nematode *Caenorhabditis elegans*, and neuronal cell lines (Hofrichter et al.,2016; Heiner et al., 2018; Chalatsa et al., 2018).

Hypothetical mechanisms of polyvalent action of GMT against stress-induced and aging-related disorders, including mild cognitive disorders, Alzheimer's disease, mood, anxiety, depression, and depressive-like behavior, are mainly based on dysregulations (Panossian, 2023):

- neurotransmitter systems, including monoamines (dopamine, norepinephrine and serotonin) (Knörle and Schnierle P. 2005; Knörle, 2012; Feistel and Walbroel, 2012; Lazarova et al., 2023); and activation of dopaminergic, norepinephrinergic, serotonergic and the cholinergic neurotransmission (Dimpfel, 2013; Dimpfel et al., 2016a; Dimpfel et al., 2016b);
- neurodegeneration and triggering of amyloid- *β* (A *β*) deposition (Hofrichter et al.,2016; Heiner et al., 2018; Chalatsa et al., 2018; Ververis et al., 2023);
- impaired neurogenesis (Tumou et al., 2023);
- chronic oxidative stress, neuroinflammation, and inflammageing (Danesi et all, 2013; Jeremic et al.,2019; Tadić et al.,2007; Tadić et al.,2007; Tadić et al.,2012a; Tadić *et al.,* 2012b).

Effects on monoaminergic-mediated neurotransmission: In 2005 Knörle and Schnierle published a patent application, where the inventors claimed that plants of the genus Sideritis prevent and influence disorders associated with altered serotoninergic neurotransmission; these include depressive disorders, chronic pain, panic attacks, generalized anxiety disorder, 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 other monoamines, including serotonin, noradrenaline, and dopamine uptake in rat brain synaptosomes and human choriocarcinoma JAR cells line (Knörle,

2012). The water and alcoholic *Sideritis* species extracts inhibited the uptake of monoamines into rat brain synaptosomes by their corresponding transporters in the EC50 30-40 μg/ml range. Inhibition of the human serotonin transporter by the extract was even more effective (EC50 1.4 μg/ml), suggesting their potential use in mental disorders associated with malfunctioning monoaminergic neurotransmissions, such as anxiety disorders, major depression, attention-deficit hyperactivity disorder, cognitive impairment, or neurodegenerative diseases (Knörle, 2012). These results were unrelated to the distinct used *Sideritis* species nor of their origin (Panossian, 2023).

Further studies were conducted with pharmaceutical Quality grade ethanolic-water *S.scardica, S.raiseri, and S.euboa* extracts preparation and aqueous tea-analog preparation (nutrifn®mental) *in vivo* study in mice to detect psychopharmacological effects assessed by their brain electrical activity recorded by Electro EncephaloGraphic Phraseogram (EEGP) (Walbroel and Feistel, 2010; Walbroel and Feistel, 2011; Feistel and Walbroel, 2011, Dimpfel 2013). Stereotactic implantation of four semi-microelectrodes into rats' frontal cortex, hippocampus, striatum, and reticular formation allowed continuous wireless monitoring of field potentials (EEG) before and after drug intake. After frequency analysis (Fast Fourier Transformation), electric power was calculated for six ranges (delta, theta, alpha1, alpha2, beta1, and beta2). The most substantial effects were observed in alpha2 waves, which are related to an activation of dopaminergic neurotransmission; delta, theta, and alpha1 waves were also attenuated, suggesting the activation of the cholinergic, norepinephrinergic, and serotonergic transmission systems. All activities were located in the frontal cortex and hippocampus regions responsible for cognitive performance (Walbroel and Feistel, 2011; Dimpfel, 2013). All extracts were given orally by gavage dissolved or dispersed in water (1 ml/kg weight). The dose of *S.scardica* extract (extraction solvent – 20 % ethanol, DER 5–9:1, containing 0.5–1.5% flavonoids, 0.1–0.4% caffeoylquinic acids, Finzelberg GmbH & Co. KG, D 56626 Andernach, Germany) corresponded to a recommended human dose of 800-1200 mg (Panossian, 2023). Dosages were chosen by considering the human dose recommendation and a relationship factor of 5–10:1 based on kilogram body weight (Dimpfel, 2013).

Sideritis scardica 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 plant extract was orally administered in the daily dose of 6000 mg/kg (corresponding to 30g of human dose) for 11 consecutive days in the presence or absence of scopolamine (1 mg/kg, i.p) (Panossian, 2023). In these experiments, the *Sideritis scardica* water extract prevented the attenuating of noradrenalin and serotonin levels in the brain of mice with scopolamine-induced neurodegeneration in the dementia model; however, it did not affect scopolamine-reduced acetylcholinesterase activity (Lazarova et al., 2023).

In a similar study Lazareva et al.,2024, compared the potential effect of *Sideritis scardica* lower dose (200 mg/kg, *p.o.* corresponding to 1 g of human dose*)* with

C. vulgare (100 mg/kg, *p.o.)* on learning and memory in healthy and scopolamine Scopoletin-induced memory-impaired male Wistar rats over a 21-day period. Both extracts effectively mitigated Scopoletin-induced memory impairment and alleviated Scopoletin-induced downregulation of p-CREB/BDNF signaling, suggesting neuroprotective mechanisms. Their combination significantly improved recognition memory and maintained monoaminergic function. *S. scardica* was superior in preserving spatial working memory (Lazareva et al., 2024).

Overall, *Sideritis scardica* hydroalcoholic extracts inhibit neurotransmission of serotonin, noradrenaline, and dopamine, suggesting potential use in mental disorders such as anxiety disorders, major depression, attention-deficit hyperactivity disorder, cognitive impairment, or neurodegenerative diseases (Knörle, 2012; Feistel and Walbroel, 2012; Panossian, 2023).

Effects on amyloid-β triggering neurodegeneration: The main feature of Alzheimer's disease (AD) is a progressive loss of memory and cognitive abilities. The crucial pathogenic step of neurodegeneration and progression of AD is amyloid- *β* (A *β*) deposition as a neuritic and extracellular diffuse plaque, intracellular tau protein in the form of neurofibrillary tangles, and brain atrophy.

Daily oral treatment with dried ethanol 20% extracts of *Sideritis scardica*, and *Sideritis euboea,* as well as their 1:1 combination (Finzelberg GmbH & Co. KG, Andernach, Germany), enhance memory and learning in Alzheimer's disease (AD) induced amyloidosis mouse models in APP-transgenic and aged C57Bl/6 mice (Hofrichter et al., 2016). The raw herb material (residual humidity of < 12%) was extracted exhaustively 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-suspended in water and applied by daily gavage at the age of 40 days (AD-initiation) or 50 days (post-AD onset), respectively, up to the age of 100 days. (Hofrichter et al., 2016). The extracts were applied in two dosages: 1.2 g/kg body weight (AD initiation) and 12 g/kg body weight (post-AD-onset) (Panossian, 2023). Non-transgenic mice were treated for 15 days (short-term) with an intermediate dosage of 6 g/kg body weight of the *Sideritis* extract combination, starting at the age of 135 days for 15 consecutive days until the age of 150 days (first period), and repeatedly for three further periods of 15 days at ages 300, 450, and 600 days, respectively (Hofrichter et al., 2016). *Sideritis* species extracts improve memory performance in APP-tg mice; improve retentiveness, learning aptitude, and decreased escape latency values of mice treated post-AD-onset with *Sideritis* species extracts compared to vehicle-treated control mice indicate increased spatial memory. The improvement of cognition functions was associated with histomorphological and biochemical changes related to the deposition of soluble amyloid-β (Aβ), which recognized triggers of the disease. The treatment with *Sideritis scardica* extracts strongly reduced Aβ42 load in mice, accompanied by the increased phagocytic activity of microglia, increased expression of the α-secretase, and fully rescued neuronal loss of mice to normal levels by affecting Aβ pathology and cognitive decline (Hofrichter et al., 2016; Panossian, 2023).

In another study, the neuroprotective activity of hydroalcoholic extracts of *S. scardica* (prepared from water, 20, 40, 50, 70% ethanol, and unipolar fractions were prepared from the 40% ethanolic extract; Finzelberg GmbH & Co. KG, Andernach, Germany) has been demonstrated in *Caenorhabditis elegans* nematode used as a model for Alzheimer's disease associated with amyloid-β aggregation and toxicity (Heiner et al. 2018). The exposure of the extracts in transgenic *C. elegans* strains expressing amyloid-β resulted in a reduced number of peptide aggregates in the head region of the worms. It alleviated 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-induced paralysis by up to 3.5 h (Heiner et al. 2018).

Sideritis scardica methanolic extract exhibited beneficial effects against amyloidogenic and Tau misprocessing pathways in Alzheimer's Disease neuronal cell culture models, including the human neuroblastoma overexpressing SH-SY5Y-AβPP and the hyperphosphorylated tau expressing rat pheochromocytoma PC12-htau cells via decreasing the activation of the GSK3β, ERK1, and ERK2 kinases of tau, and by tau hyperphosphorylation. The extracts appear to promote AβPP processing through the alpha, non-amyloidogenic pathway, suggesting that *S. scardica* can prevent or inhibit the progression of AD (Chalatsa et al., 2018; Panossian, 2023).

Recently Ververis et al. 2023 compared the neuroprotective activity of eight fractions of *Sideritis scardica* water extract in SH-SY5Y human neuroblastoma cells treated with highly neurotoxic amyloid Aβ25–35 peptides. Four of the eight fractions statistically inhibited neurotoxicity; the most active was initial aqueous extract in concentrations of 50–200 μg/mL, characterized as riches of neuroprotective substances, such as apigenin, myricetin-3-galactoside, and ellagic acid (Ververis et al., 2023).

Neurogenic Activity: The neurogenic potential of *Sideritis scardica* areal part water infusion was found as potent as a classical neuronal inducer, the combination of retinoic and valproic acid (c = 10/50 μM, positive control), promoting the generation of new neurons, assessed by differentiation-inducing and normalized *Renilla* activity assays in mouse embryonic forebrain cells (Tumou et al., 2023; Panossian, 2023). Concentration-dependent study of cytotoxicity of eighth *Sideritis* ssp. dried infusions were found IC50 in the range of 163 to 322 μg/mL in thrice-subcloned SH-SY5Y cell line culture derived from the SK-N-SH neuroblastoma cell line, which is widely used as a model for neurodegenerative diseases. The IC50 cytotoxic concentration of *Sideritis scardica* was 320 μg/mL. Metabolomic fingerprinting of eight analyzed Sideritis taxa showed that phenylethanoid glycosides (trans-verbascoside and trans-leucosceptoside A) and flavonoid glycosides (isoscutellarein 7-O-[6‴-O-acetyl- β -D-allopyranosyl]-(1 → 2)- β -D-glucopyranoside and apigenin 7-O-[6″-O-trans-p-coumaroyl]- β -Dglucopyranoside) are presumably principal components of the genus *Sideritis* suggesting that they contribute for the effect on the cell viability of SH-SY5Y neuroblastoma cells (Tumou et al., 2023).

8.2 Antimicrobial Properties

Various *Sideritis scardica* Griseb. extracts and their fractions have been studied for its antimicrobial properties against Gram-positive bacteria, *Streptococcus pyogenes, Streptococcus canis, Moraxella catarrhalis, Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus,* 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*. The strong to moderate antimicrobial activity of all investigated extracts was demonstrated in the minimal inhibitory concentration in the range from 40 to 2.56 µg/ml. Maximum activity was observed against *S. epidermidis*, *M. luteus, E. coli,* and *P. aeruginosa*, and moderate activity against *K. pneumonia*. The antimicrobial activity of the extracts was similar regardless of differences in their chemical compositions (Tadić et al.,2007; Tadić et al.,2012a; Yaneva & Balabanski, 2013; Panossian, 2023).

8.3 Gastroprotective and Inflammatory Effects

Gastroprotective and inflammatory effects of the ethanol, diethyl ether, ethyl acetate, and *n*-butanol extracts of *Sideritis scardica* were studied in ethanol-induced acute gastric damage in rats in the doses of 50–200 mg/kg (*p. o.)* using ranitidine (5–20 mg/kg, *p. o.*) and indomethacin (4 mg/kg, *p. o.*), as reference drugs. All examined extracts produced dose-dependent gastroprotective activity with an efficacy comparable to that of the reference drug ranitidine. Diethyl ether and *n*-butanol extracts reduced the rat paw edema in the doses of 100 and 200 mg/kg (to 53.6 and 48.7%; 48.4 and 49.9%, respectively) comparably to indomethacin reducing 50% effect (Tadić *et al.,* 2012b).

9. SECONDARY PHARMACODYNAMICS

Antioxidant activity: *Sideritis scardica* extracts were compared with *Sideritis syriaca, Sideritis montana* extracts, and two reference antioxidants - hydroxytoluene (BHT) and rosmarinic acid by the β-carotene bleaching test (BCBT) and 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging test. The most potent antioxidant effect was observed for the apolar extracts similar to that of BHT in the β-carotene bleaching test. In contrast, the polar extracts and rosmarinic acid were less potent than those of BHT. The inhibition of hexanal formation in bulk safflower oil by *Sideritis scardica* 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 against DPPH-induced oxidation was similar to that of rosmarinic acid (Koleva et al., 2003). The DPPH-induced radicals scavenging assays revealed that *Sideritis scardica* and other *Sideritis* ssp (*Sideritis clandestina* subsp*. clandestina, Sideritis euboea, Sideritis perfoliata* subsp. *perfoliata, Sideritis raeseri* subsp. *raeseri,* and *Sideritis syriaca*) extracts exhibited substantial antioxidant activity (% inhibition >74 at 300 µg/ml) (Papaefstathiou et al., 2014; Panossian, 2023).

The antioxidant potential of *Sideritis scardica* extract was compared to *Camellia sinensis* extract in HepG2 cells. The *S. scardica* fresh leaves (extraction solvent - 70% methanol at 70◦C, DER 8:1; Indena, Milan, Italy) were specified by the manufacturer as containing a polyphenol content of 75 ± 5 %, an EGCG content of 30 ± 5 %; content of other catechins of 40 ± 100% g and a caffeine content <8% (Danesi et al., 2012). Although *Sideritis scardica* extract had a lower phenolic concentration and total antioxidant capacity than *Camellia sinensis* extract, their cellular antioxidant effects were similar. The different phenolic pattern of the extracts suggests that the protective activity is not limited to catechins (Danesi et al., 2012).

Anti-aging effects: The anti-aging potential of *Sideritis scardica* was compared with *Plantago major* and propolis extracts produced by so-called Natural Deep Eutectic Solvents (NADES) in lifespan experiments in four Saccharomyces cerevisiae yeast strains-a wild type and three chromatin mutants exhibiting characteristics of premature aging. The extract ameliorates their cellular growth and cell cycle and influences the activity of some stress-responsive genes. (Vasileva et al., 2022; Panossian, 2023)

About 6000 plant species growing in Greece were selected to identify plants that can delay cellular senescence by regulating age-related signaling pathways in senile skin, which is characterized by substantial 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-melanogenic properties as a preferable source of photoprotective agents against skin hyperpigmentation. The most promising 4% of the extracts were chemically and pharmacologically characterized in vitro and cell-based assays covering most of the parameters contributing to skin aging. In particular, the methanolic extracts of *Sideritis scardica* and *Rosa damascena* showed promising effects against specific targets involved in skin aging (Sklirou et al., 2021).

Cytotoxic and antitumor activities: Cytotoxic potential of ethanol, diethyl ether, ethyl acetate, *n*-butanol extracts of *Sideritis scardica,* and major phenolic compounds of the extracts was studied in PBMC, B16 melanoma, and HL-60 leukemic cells. Only diethyl ether extract triggered 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 100 µg/ml. The main cytotoxic flavonoids were luteolin, apigenin-7-0-ß-glycoside, apigenin, and luteolin-7-0-ß-glycoside. (Tadić et al., 2012b; Jeremic et al., 2013; Panossian, 2023).

In vitro cultivated *Sideritis scardica* grown in the field revealed a higher total polyphenol content and higher antioxidant activity than *in situ* cultivated plants. A comparison of the antitumor activities of extracts from *in vitro* propagated shoots, field-grown in vitro-obtained plants and *in situ* plants on HeLa (cervical adenocarcinoma), HT-29 (colorectal adenocarcinoma) and MCF-7 (breast cancer) human cancer cell lines showed that *in vitro* propagated shoots had a significant concentration-dependent cytotoxic effect on the cervical adenocarcinoma cell line HeLa, while the field-grown in vitro-obtained and in situ-

collected samples induced the highest reduction in the viability of the mammary carcinoma cell line MCF-7 (Tasheva et al., 2023).

Anti-obesity and anti-diabetic properties: A study of the effects of *Sideritis scardica* aqueous extract on metabolic disorders induced by ovariectomy in rats aimed to assess their food intake, weight gain, body composition, fasting glucose levels, response to oral glucose challenge, liver glycogen content, catalase activity, thiol groups, malondialdehyde concentrations, as well as AMP-activated protein kinase activity in liver cells. Administration of *S. scardica* extract (200 mg/kg daily for 24 weeks) lowered blood triglycerides, reduced fasting glucose levels and blood glucose peaks after oral glucose challenge, increased liver glycogen content, and significantly higher catalase activity and thiol group concentration in ovariectomized rats. The authors conclude that *S. scardica* extract attenuates metabolic disturbances in rats, suggesting possible therapeutic benefits for diabetes, obesity, and postmenopausal women, with increased risk for breast and endometrial cancer and a risk for cardiovascular and thromboembolic disease (Jeremic et al., 2019).

Pharmacokinetic: The primary aim of pharmacokinetic studies of herbal preparations comprising multi-component intervention is to trace their absorption and distribution in body tissues, metabolism, and elimination after oral administration to estimate concentrations matching effective concentrations found in pharmacodynamic studies.

Metabolism of polyphenols and their urine excretion was studied in 10 healthy human subjects after single-dose administration of 8 g *Sideritis scardica* decoction 300 mL of Herba Sidetiris decoction. Thirty-one metabolites of hypolaetin, methyl-hypolaetin, isoscutellarein, methyl-isoscutellarein, apigenin, and 32 phenolic acid metabolites were quantitatively analyzed and validated by HPLC-DAD-ESI-MS/MS method. In a total of 63 glucuronides and sulfated metabolites of flavonoids (hypolaetin, isoscutellaerin, and apigenin) derivatives and hydroxycinnamic acid derivatives (quinic, caffeic, chlorogenic, ferulic, and coumaric acids) were identified in excreted in human urine collected for 24 h after oral administrated 300 mL of Herba Sidetiris decoction (Petreska Stanoeva and Stefova, 2013; Panossian, 2023).

A comparison of the composition of hydroxycinnamic acid derivatives of *Sideritis* decoction containing only four hydroxycinnamic acid derivatives, with their urine excretion, showed the presence of 32 hydroxycinnamic acid metabolites (5 quinic acid derivatives, five caffeic acid derivatives, seven caffeoylquinic acid derivatives, eight ferulic acid derivatives, three dimethyl ferulic acid derivatives, three feruloyl quinic, acid derivatives, and two coumaric acid derivatives, presumably due to interactions with the intestinal and/or hepatic detoxification enzymes.

The total content of phenolic metabolites in urine samples was determined as a sum of the total content of metabolites from hydroxycinnamic acid derivatives, apigenin, hypolaetin, and isoscutellarein. The total amount of hydroxycinnamic

acid derivatives in urine samples ranged from 1.714 to 33.62 μ mol, which corresponds to 5.24−18.18% (n/n) of total metabolites excreted in urine and around 1.5% of the ingested dose of total phenolics present in 300 mL of the *Sideritis* decoction. Total metabolite content in urine after 24 h was in the range from 32.73 to 184.9 μ mol, which represents 1.46−8.24% (n/n) of the total phenolic content present in the 300 mL of *Sideritis* decoction ingested. The most abundant urinary metabolites were methyl-hypolaetin and methyl-isoscutellarein glucuronides, excreted mainly from isoscutellarein and apigenin (Petreska Stanoeva and Stefova, 2013; Panossian, 2023).

Further studies are required to estimate active doses and blood concentrations of principle compounds of GMT or their metabolites targeting the body tissues in matching effective concentrations, particularly crossing the blood-brain barrier.

10. PRECLINICAL SAFETY

Acute and repeated-dose oral toxicity: A *Sideritis* herb dry extract (70% native, 30% maltodextrin; extraction solvent: 20% V/V ethanol) has been tested 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 or mortality could be detected in all six female rats throughout the study period of 14 days when treated at the dose level of 2000 mg/kg of the test item. The tested *Sideritis* herb extract has been assigned to category 5, covering the range for oral LD 50 to be 2000 mg/kg- 5000 mg/kg body weight. The repeated-dose toxicity of the extract was studied by its daily oral administration of rats by gavage in dosages of 250 mg/kg, 500 mg/kg, and 1000 mg/kg body weight for 28 days, followed by a 14-day recovery period 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. No mortality or changes in body/organ weight or food consumption have been observed. The sensory reactivity of auditory, visual, and proprioceptive stimuli did not show abnormalities in the treatment and control groups. Hematological analysis also revealed no abnormalities except for an increase of the MCV and MHCH values at the dose of 1000 mg/kg in males and the case of platelets at 1000 mg/kg in female rats. 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 were only marginal. No hematological changes have been caused by the *Sideritis* extract, except for a decrease of MCH in female animals from the 1000 mg/kg reversal group sacrificed on day 43, but estimated to be in the biological range (Panossian, 2023). Concerning the clinical, biochemical parameters of Calcium and sodium (250 mg/kg, 500 mg/kg, and 1000 mg/kg, male), Chloride (250 g/kg and 1000 mg/kg, female), and Sodium (500 mg/kg and 100 mg/kg, female) have been marginally influenced by the test item. The organ weight of the tested rats from different dose and control groups and that of the reversal group (1000 mg/kg) did not differ.

Moreover, the pathological and histopathological examinations did not indicate any abnormalities that could be referred to the treatment with the *Sideritis scardica* dry extract. The extract's no-observed-adverse-effect level (NOAEL) was determined at 1000 mg/kg body weight in male and female animals when the Sprague Dawley rats were treated over 28 days in this repeated dose oral toxicity study. The study reveals no toxicity of *S. scardica*, supports its favorable safety profile, and confirms the acknowledged traditional medicinal use in humans (Feistel et al.2018; Panossian, 2023).

In a recent study of subchronic toxicity of dry methanolic (70%) extract of *S.scardia* (total polyphenols, 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 of 100, 200, and 400 mg/kg (Yanchev et al., 2023). The subchronic toxicity experiment follows up an acute toxicity assessment in which no lethality was observed after a single oral administration of 1000, 2000, 5000, and 10000 mg/kg doses. All hematological and biochemical results remained within the normal reference ranges described for the species. All hematological, biochemical, and histological examinations showed no abnormalities, including in the morphology of the examined organs (brain, stomach, liver, and kidney).

Genotoxicity: 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 (EMEA/HMPC/67644/2009; EMA/HMPC/39455/2015) (Panossian, 2023).

Four Ames tests with the dry extracts from *Sideritis scardica* herb of different polarity:

a. 70% native, 30% maltodextrin; DER native: 4-8:1; extraction solvent water,
b. 70% native, 30% maltodextrin; DER native: 7.2:1; extraction solvent 20% (V/V) ethanol,
c. 70% native, 15% maltodextrin,15% silica; DER native: 6:1; extraction solvent 50% (V/V) ethanol,
d. 50% native, 50% silica; DER native: 83:1; extraction solvent heptane

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 four extracts of different polarities were negative (Feistel et al.2018). The water *Sideritis* extract (a) 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 (EMA/HMPC/39455/2015). The study reveals no concerns about the mutagenic effects of all four extracts, covering the entire spectrum of phytochemical constituents of the *Sideritis scardica* herb, including polar and non-polar constituents. (Feistel et al.2018; Panossian, 2023).

Carcinogenicity: No carcinogenicity studies have been conducted on *Sideritis scardica* in the scientific literature.

Reproductive and developmental toxicity: No reproductive and developmental toxicity studies on *Sideritis scardica* were found in the scientific literature.

11. CLINICAL PHARMACOLOGY – CLINICAL TRIALS

11.1 Cognitive and Anxiety Disorders

Neurodegeneration-associated cognitive disorders, including Alzheimer's disease and mild cognitive impairments (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, et al., 2020). Anxiety can also cause cognitive disorders symptoms, such as difficulty concentrating, fatigue, increased heart rate, and other symptoms (Panossian, 2023).

Recent clinical studies aimed to assess the efficacy of several preparations of *Sideritis scardia* on the cognitive function of healthy individuals in a stressful environment (Behrendt et al., 2016) and elderly adults with MCI and anxiety (Dimpfel et al., 2016a; Dimpfel et al., 2016b; Wightman et al., 2018). In addition to the cognitive performance, the patient's mood, cerebral blood flow, blood pressure, and brain electrical activity were studied in detail.

Cognitive functions of healthy subjects in stress: An herbal extract of *Sideritis scardica* (330 mg of an alcoholic aqueous extract, Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany), vitamin B1 (0.55 mg), vitamin B6 (0.7 mg), Vitamin B12 (1.25 µg), and folic acid (100 µg) was studied in an open-labeled trial in 64 healthy 25-60 years old participants taking the supplement orally twice daily for six weeks (Behrendt et al., 2016).

The study aimed to assess the efficacy of a fixed combination of *Sideritis scardica* with vitamin B complex to reduce stress-induced impairment of working memory, cognitive flexibility, and controlled behavior and improve stress tolerance. The cognitive performance of healthy subjects was assessed by the so-called Trail-Making test (TMT), by concentrating their attention and short memory by linking randomly scattered numbers and alphabetic characters and the Color-Word-Test (CWT, *syn.* Stroop-Test) before and after an acute stress stimulus, including noise and mental load (CWT) interference (Panossian, 2023). The validated Perceived Stress Questionnaire (PSQ) was also used to assess the subjective chronic stress perception on emotional and cognitive levels in the study participants. TMT was not feasible for measuring any intervention's stress-relieving or attention-promoting properties because the intra-assay controls did not comply with the assumptions concerning the accuracy of this test. In contrast, the CWT and PAQ proved suitable for assessing the influence of stress-induced impairments; CWT reaction time after six weeks of product 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 upon product intake.

The authors concluded that dietary supplementation of *Sideritis scardica* with vitamin B can alleviate stress-induced impairment, improving working memory and cognitive flexibility. (Behrendt et al., 2016). The authors suggested that the combination of *Sideritis scardica* with vitamin B may be relevant for persons solving cognitive tasks under conflict and/or noise (e.g., open-plan offices or car-driving) and support that the tested product alleviates stress-induced impairment of executive functioning (working memory, cognitive flexibility, controlled behavioral inhibition) (Behrendt et al., 2016).

The study limitations include the lack of a placebo group or blinding since a study design without a control group is often deemed insufficient for formal proof, which can be achieved by a randomized, double-blind, controlled trial (Panossian, 2023).

Cognitive functions of elderly patients with mild cognitive impairments: Two publications described a study of *Sideritis scardica* of dry extract (extraction solvent – 20 % ethanol, DER 5–9:1, containing 0.5–1.5% flavonoids 0.1–0.4% caffeoylquinic acids), and its combination with *Bacopa monnieri* extracts (memoLoges®, Dr. Loges GmbH, Winsen, Germany) in elderly adults with mild cognitive impairments (Dimpfel et al., 2016a; Dimpfel et al., 2016b).

Acute effects of a single dose of 500 mg of *Sideritis scardica* of dry extract and its combination with *Bacopa monnieri* 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 of multiple of administration of the combination of 500 mg of *Sideritis scardica* of dry extract and its combination 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 an 18-point dementia scale in the range from 8 scores (severe dementia) to 13 scores above ("normal" cognitive performance) (Panossian, 2023).

Efficacy measures were assessed by quantitative EEG recording and psychometric tests, including:

- The so-called "paper-pencil d2-test" of the ability to concentrate is when the patients have to mark all "d" spelling letters with two adds for 20 seconds in each line under the condition of EEG recording.

- The "concentration-performance-test" (CPT) targets the performance of arithmetic when the patients memorize the transitory results of the first task to be processed after the performance of the second task.
- 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 seconds during which the screen remained dark, and a four-fold multiple choice, including the correct answer, was presented for decision. The number of tasks and % correctness were evaluated to evaluate as a performance index.

Single dose effect of *Sideritis* extract alone or in combination with *Bacopa* extract (memoLoges®) led to statistically significant improvement in concentration, increasing the attention of patients in the d2-concentration test. Quantitative EEG spectral maps recorded under the different experimental conditions displayed enormous differences between both extracts. *Sideritis* extract and its combination with a low amount of *Bacopa* extract (160 mg) induced increasing spectral power in frontotemporal brain areas compared to placebo. A different activity of both extracts was confirmed by discriminant analysis (Dimpfel et al. 2016a; Panossian, 2023).

The effect of multiple administrations of the combination of *Sideritis scardica* and *Bacopa monnieri* extract (memoLoges®) in patients with MCI for four weeks was similarly assessed by psychometric tests (d2-concentration test, arithmetic calculation test, and a memory test and Quantitative EEG recording on the first day and one day after the last repetitive administration. Intake of memoLoges® induced a trend of performance improvement in all three psychometric tests, suggesting that a combination of *Sideritis scardica* and *Bacopa monnieri* extract can improve concentration and short memory. EEG data analysis revealed attenuation of delta and theta spectral power in the frontal brain, similar to what was reported in the EEG pattern of the Alzheimer drug rivastigmine, "normalizing" the spectrum. The combination of *Sideritis scardica* and *Bacopa monnieri* statistically significantly increased beta power on the background of mental load, suggesting a positive effect in MCI patients. (Dimpfel et al. 2016b; Panossian, 2023).

Effect on memory, attention, mood, and cerebral blood flow in anxiety of elderly adults: 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 memory, and raised visual sustained attention. (Wightman et al., 2018). Exclusion criteria were high blood pressure, history of neurological, vascular, or psychiatric illness, current diagnosis of anxiety or depression, and any health condition that would prevent the fulfillment of the study requirements.

A final dataset of N = 140 was arrived at for the cognitive analyses. Data catchment errors resulted in a sample of N = 142 for the mood (State-Trait Anxiety Inventory (STAI)) analysis.

The aim of the randomized, double-blind, placebo-controlled, parallel groups trial was to assess the efficacy of *Sideritis scardica* dry extract in two daily doses of 475 mg and 950 mg compared to active control (*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 at Day 1) and repeated administration (two capsules daily, one in the morning, advised "with breakfast," and one capsule in the evening advised "with evening meal") for four weeks (an accumulative effect of 28 days of treatment on Day 28). *Sideritis scardica* dry extract was specified for 6.25% phenolic content containing 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 (Finzelberg GmbH & Co. KG, Martin Bauer Group, Germany) (Panossian, 2023).

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

- Speed (msecs) and Accuracy of Episodic Memory (% correct), derived from outcome measures of individual cognitive tasks, including Delayed word and Picture’ Recognition and Delayed Name/Face and Word Recall.
- Working Memory (% correct), delivered from outcome measures of individual cognitive tasks including Numeric Working Memory and Cognitive Demand (working memory executive function attention) battery including Rapid Visual Information Processing (RVIP) and Bond Lader Visual Analog Scales (VAS).
- Speed (msecs) and Accuracy of Attention (% correct) - Choice Reaction Time task.

Mood outcome measures were assessed by the Bond-Lader mood and the State-Trait Anxiety Inventory during the training and screening visits to provide a baseline measure of mood.

The blood pressure readings and cerebral blood flow were monitored using a frequency domain "quantitative" Near-Infrared Spectroscopy system, providing absolute measurements of oxygenated hemoglobin (HbO2), deoxygenated hemoglobin (HHb), total hemoglobin (tHb; HbO2 + HHb) and oxygen saturation (Ox%; HbO2/tHb × 100%) for quantifying acute changes in hemodynamic response in Cerebral circulation flow and over an extended period between Day 1 and Day 28 (Panossian, 2023).

Compared to the group given a placebo and active comparator group given, the patients that received GMT observed the following improvements:

- Improved mood and Reduced anxiety state, Mood—State-Trait Anxiety Inventory (STAI): GMT,950 mg/475mg *vs.* placebo and Gingko, single effect on Day 1 and repeated administration for four weeks
- Greater ability to recognize pictures (% correct): GMT,950 mg vs Gingko, single effect on Day 1 and repeated administration for 4 weeks
- Enhanced information processing (Processing False Alarms (number): GMT,950 mg vs placebo, repeated administration for 4 weeks
- Increased reaction speed (Speed of Attention (milliseconds): GMT,950 mg/475mg *vs.* Gingko, single effect on Day 1 and repeated administration for 4 weeks
- Greater ability to remain focused and access working memory,
- Improved overall cognitive performance,
- Increased transport of blood oxygen from the lungs to all other body tissues, including the brain.
- Improved blood flow to the brain's prefrontal cortex—the part of the brain associated with cognitive behavior, personality expression, decision-making, and appropriate social behavior.

The most evident effects of GMT in the daily dose of 950 mg, compared to placebo, were improved cognitive function, significantly reduced false alarms in rapid visual information processing test after 28 days of treatment, and reduced anxiety compared to Gingko and placebo (Panossian, 2023).

Both doses of GMT revealed significantly greater oxygen saturation, increasing oxygenated hemoglobin (Ox%) in the prefrontal cortex during the completion of cognitively demanding tasks on Day 1, with the lower 475 mg dose producing the most pronounced effect. In comparison, Ginkgo was associated with lower saturation. The higher dose showed more significant total and deoxygenated hemoglobin levels on Day 1. Still, no further effects were seen on cerebral blood flow after repeated administration for four weeks. Surprisingly, the single dose effect of Ginkgo decreased levels of Ox% and increased levels of Hb and reduced levels of both HbO and THb after treatment for four weeks.

The authors conclude that significantly improved cognitive performance following GMT on Day 1 could be due to significant modulation of the cerebral blood flow response. In contrast, the improvements in mental performance on Day 28 are likely due to decreased state anxiety, suggesting promoting to underpin more prolonged cognitive improvements (Wightman et al., 2018; Panossian, 2023).

Metabolic Health and Redox Biomarkers in Healthy Adults: The effect of lyophilized water extract of *Sideritis scardica* areal parts (SidTea+TM) on the physiological profile, metabolic health, and redox status was studied in 28 healthy adults in a randomized, double-blind, placebo-controlled trial. Participants took SidTea+TM capsules in a daily dose of 1500 mg/day for four weeks (Papanikolaou et al., 2024). At the end of four weeks of supplementation,

SidTea+TM significantly decreased systolic blood pressure (−10.8 mmHg), mean arterial pressure (−4.5 mmHg), resting heart rate (−3.1 bpm) handgrip strength of the non-dominant limb (−0.8 kg), an increase VO2max (+1.1 mL/kg/min), a reduction in γ-GT and SGPT enzymatic activity in serum (−3.7 and −3.3 U/L, respectively), increased total antioxidant capacity and decreased lipid peroxidation levels in plasma compared to the baseline values. However, a comparison of baseline outcome measures in placebo and SidTea+TM supplemented groups showed significant differences concerning body weight, BMI, systolic blood pressure, cardiorespiratory capacity eVO2max, handgrip strength, metabolic markers, redox markers, and other indices indicating unsuccessful randomization of intervention and placebo between study groups and on risk of bias (Papanikolaou et al., 2024). At baseline, the placebo group participants had higher body weight, BMI, systolic blood pressure, cardiorespiratory capacity eVO2max, handgrip strength, metabolic markers, redox markers, and other indices. Regardless of the cause of this disbalance due to lack of proper randomization and insufficient sample size, the effects of SidTea+TM and placebo cannot be adequately compared because, at baseline, there is a difference between the two groups. The beneficial effect of supplementation was not supported with statistically appropriate methods, and the effects of interventions cannot be compared because their baselines are different. Furthermore, there are severe flaws in statistical analysis. In the comparison between groups (assessment of the therapeutic effect of the intervention), the changes from the baseline and instead of the actual values of the outcome measures were not compared.

The risk bias and quality scores: The risk bias and Quality scores of two available randomized placebo-controlled trials assessed by Cochrane (Higgins et al., 2011), Jadad (Jadad et al., 1996), and CONSORT (Gagnier et al., 2006) criteria are shown in Table 1 (Panossian, 2023).

Preliminary studies have indicated that GMT may enhance memory and cognitive function, improving attention, focus, and overall mental performance. Recent research has revealed that GMT contains a variety of bioactive compounds, which have been linked to mental enhancement, improvements in cognitive performance, and neuroprotective effects, potentially reducing the risk of age-related cognitive decline and neurodegenerative disorders (Panossian, 2023).

Clinical assessment of herb-drug interaction: Drug consumption of the aerial parts of *S. scardica* decoction is unlikely to result in herb-drug interactions involving the enzymes studied, except for potential herb-CYP2A6 substrate interaction in males (Begas et al., 2018).

Table 1. The risk bias, reporting, and quality scores of two available randomized placebo-controlled trials assessed by Cochrane (Higgins et al., 2011), Jadad (Jadad et al., 1996), and CONSORT (Gagnier et al., 2006) criteria

Study author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases (industry funding, conflicts of interest, etc.).	Jadad's Quality score	Interventions reporting
Dimpfel et al., 2016b	?	?	?	?	⊕	⊕	—	1	?
Wightman et al., 2018	⊕	?	⊕	?	⊕	⊕	—	4	⊕ ?
Papanikolaou et al., 2024	⊕	⊕	⊕	?	?	—	—	4	⊕ ?

Low risk of bias ⊕ *High risk of bias* — *Unclear risk of bias* ?

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

Contraindications: Hypersensitivity to the active substance and other plants of the *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 the symptoms worsen during the medicinal product use, a doctor or a qualified health care practitioner should be consulted (EMA/HMPC/39453/2015).

11.2 Precautions

Pregnancy, fertility, and lactation: Safety during lactation and pregnancy has not been established. Without sufficient data, use during pregnancy and lactation is not recommended. No fertility data are available. (EMA/HMPC/39453/2015).

Pediatric use: 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 other precautions: 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 for potential herb-CYP2A6 substrate interaction in males (Begas et al., 2018; Panossian, 2023)

11.3 Dosage Forms

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

Declaration of the herbal medicinal product in the SmPC: Each capsule contains 450 mg of extract (as a dry extract, refined) from *Sideritis scardica* Griseb., folium (equivalent to 2.25 g – 4.05 g of *Sideritis scardica*, DER 5–9: 1), corresponding to 6.25% polyphenols including 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 et al., 2018; Panossian, 2023).

11.4 Posology

Adults and elderly: *Therapeutic indications 1 and 2:* Traditional herbal medicinal product used to relieve cough associated with the common cold and relieve mild gastrointestinal discomfort (EMA/HMPC/39453/2015).

Single dose: 2-4 g of the comminuted herbal substance in 150-200 ml of boiling water as a herbal infusion.

Daily dose: up to 12 g daily for one week (EMA/HMPC/39453/2015).

The use in children and adolescents under 18 is not recommended (EMA/HMPC/39453/2015).

Therapeutic indication 3: Herbal medicinal product used for stress-induced impairment of cognitive function, memory, and mood (Behrendt et al., 2016; Dimpfel, 2016a; Wightman et al., 2018).

Single dose: 330 - 500 mg of the dried herbal extract (extraction solvent – 20 % ethanol, DER 5–9:1, containing 0.5–1.5% flavonoids 0.1–0.4% caffeoylquinic acids) in capsule or tablet dosage forms (Panossian, 2023).

Daily dose: 660-1000 mg (in 2 capsule or tablet dosage forms) (Behrendt et al., 2016; Dimpfel, 2016a; Wightman et al., 2018). Therapeutic Indication 3 has not yet been assessed and approved by drug authorities (EMA/HMPC/201708/2022).

Duration of use: *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, a doctor or a qualified health care practitioner should be consulted. (EMA/HMPC/39453/2015).

Therapeutic indication 2: Traditional herbal medicinal product used to relieve mild gastrointestinal discomfort. Duration of treatment – 14 days. If the symptoms persist longer than two weeks during the treatment, 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 cognitive function, memory, and mood. The duration of treatment is 4 - 6 weeks (Behrendt et al., 2016; Dimpfel, 2016a; Wightman et al., 2018).

Method of administration: Oral use (EMA/HMPC/39453/2015; Behrendt et al., 2016; Dimpfel, 2016a; Wightman et al., 2018; Panossian, 2023).

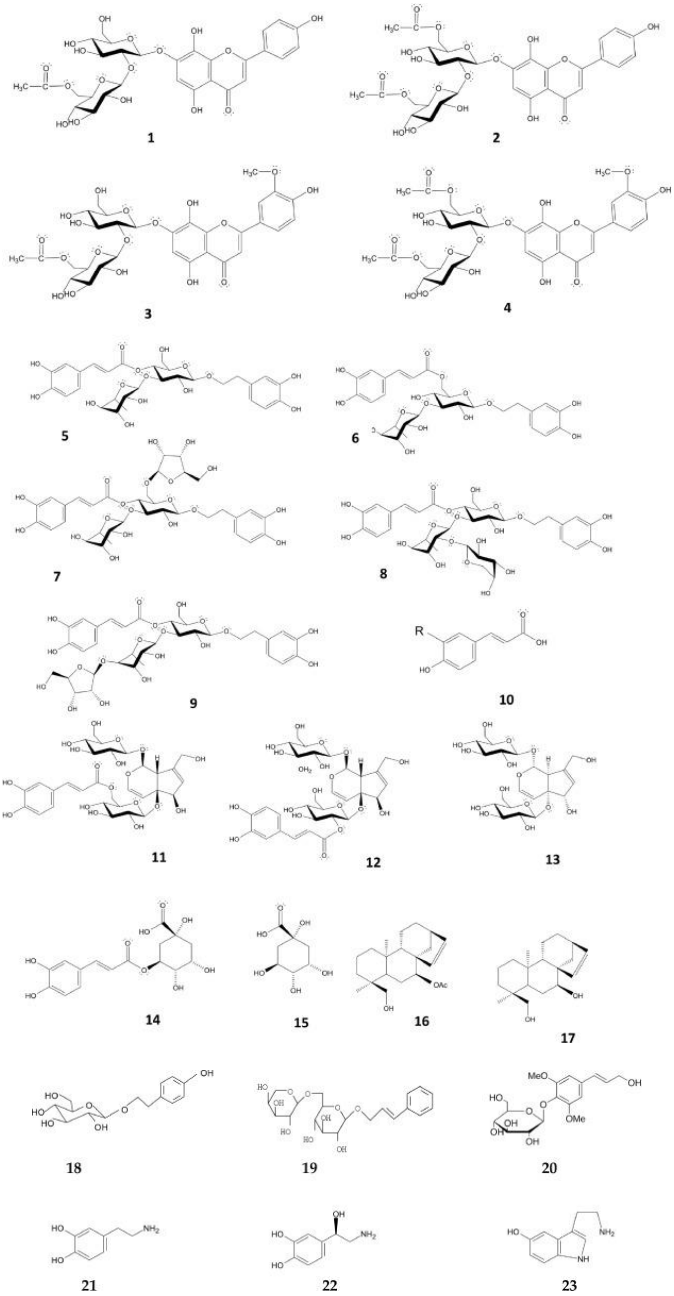
12. DISCUSSION, LIMITATIONS, AND PERSPECTIVES

Recent extensive research on GMT suggests that GMT can be characterized as a putative adaptogen, although the mechanisms of polyvalent action of GMT preparations have not been sufficiently studied in detail.
What is evident in this suggestion?

1. GMT has an excellent safety profile that is in line with the earlier definition of adaptogens (Wagner et al.1993):

- an adaptogen must be innocuous and must not influence normal body functions more than required.
- an adaptogen must have a normalizing influence independent of the nature of the pathological state;
- an adaptogen must show a non-specific activity, i.e., an increase in power of resistance against physical, chemical, or biological toxic agents,

2. Adaptogens are also known to exhibit numerous pharmacological effects associated with stress-system (neuroendocrine-immune complex, Fig. 5) and have many indications for use in stress and aging-related disorders (Panossian & Efferth, 2022; Panossian et al., 2021; Panossian 2017), including infectious diseases (Panossian and Brendler, 2020), gastrointestinal diseases (Panossian et al. 2020), Fig. 6. GMT extracts and some purified compounds isolated from *Sideritis scardica* exhibited pleiotropic 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 adaptation syndrome to stress includes a nonspecific reaction, including stomach ulceration, thymus atrophy, adrenal hyperplasia, increased secretion of cortisol and catecholamines, etc. (Panossian et al. 2020; Panossian, 2023).
3. Adaptogens have mild stress mimetic effects in the normal homeostatic range to increase the resilience of organisms and alleviate stress (Panossian et al., 2020; Anghelescu et al., 2018; Xia et al., 2016). GMT significantly increased cognitive functions and cerebral blood circulation parameters after a single administration of GMT in elderly adults but did not further improve cerebral blood oxygenation after repeated administration for four weeks, decreasing the state of anxiety and improving cognitive function, unlike Gingko, suggesting that restored homeostasis (Wightman et al., 2018).
4. The chemical composition of *Sideritis scardica* is characterized by a high content of compounds containing 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 are covalently incorporated into the chemical structures of some active principles of adaptogenic plants, such as salidroside (**18**) rosavin (**19)** in *Rhodiola rosea* (Panossian et al., 2010; Bernatoniene et al. 2023), eleuteroside B (**20**) in *Eleutherococcus senticosus* (Jia et al., 2021; Radix Eleutherococci, WHO monograph, 2002) which are structurally similar to catecholamines dopamine (**21)**, noradrenaline (**22)** and serotonin (**23)**, suggesting that these biased ligands have high affinity and allosterically compete for receptors sites of proteins involved in signaling pathways and cellular responses.
5. Acteoside (AC), found in a variety of plants, has pharmacologically useful actions for human health, including depression, neuroprotection, cardiovascular protection, hepatoprotection, bone and cartilage protection in addition to wound-healing, antibacterial, anti-fungal, anti-leishmanial, hypoglycemic, antihypertensive, anti-epileptic, anti-inflammatory, and antitumor activity in many experimental models through oxidative stress, apoptosis, anti-angiogenesis, anti-invasion, anti-metastasis, and anti-proliferative effects, and synergism with other compounds through modulation of several pathways (Alipieva et al.,2014; Khan et al.,2022; Xiao et al., 2022; Zhao et al. 2023; Panossian, 2023).



Chemical compounds: 1-23

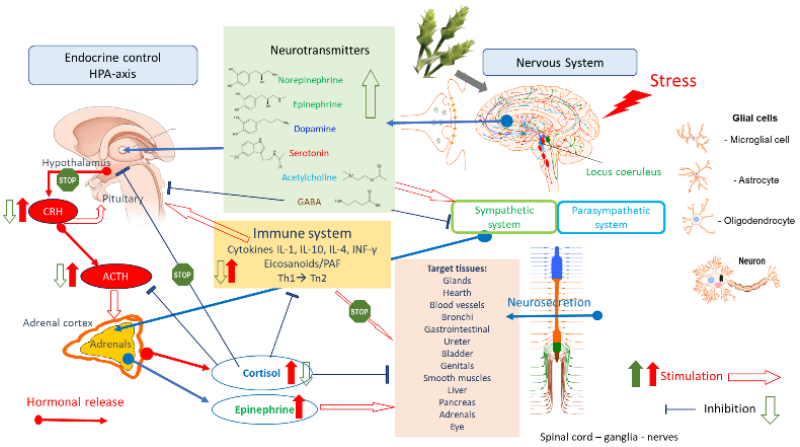
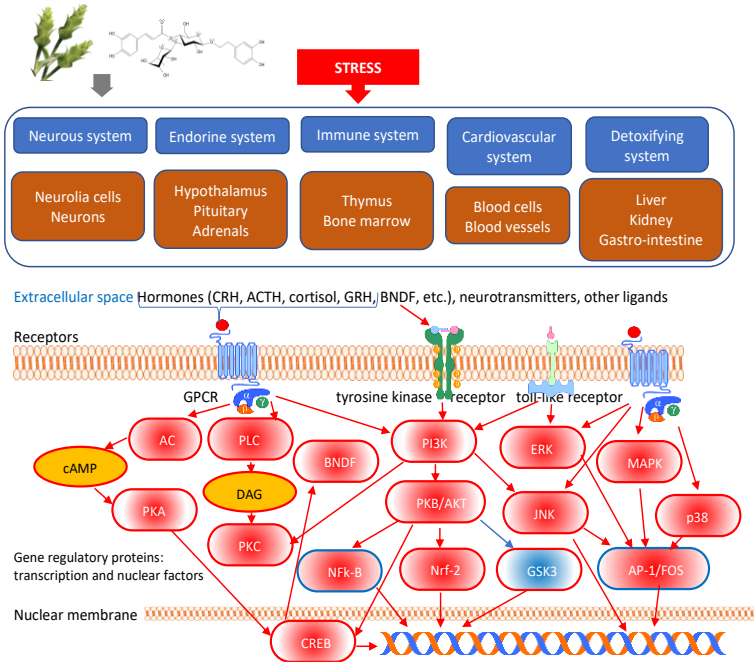


Fig. 5. Systems pharmacology of GMT: a simplified overview of the Stress System (central nervous system, CNS, and peripheral tissues/organs in the periphery) and reciprocal connections of elements of the neuroendocrine-immune complex to mobilize an adaptive response against the stressor. The brain and spinal cord comprise the CNS. The cerebral cortex comprises neurons (glutamatergic pyramidal neurons and GABAergic interneurons) and glial cells (astrocytes, oligodendrocytes, and microglia). The forebrain can be subdivided into dorsal (glutamatergic neurons) ventral forebrain (GABAergic interneurons), and LC, locus caeruleus. The peripheral components of the Stress System include (a) - the hypothalamic-pituitary-adrenal axis (HPA), (b) - the autonomic nervous system (ANS) comprised of (i) the sympathetic nervous system (SNS) secreting mainly norepinephrine (NE) and acetylcholine (AcCh); and sympathy-adrenomedullary (SAM) system, and (ii) the parasympathetic nervous system (PNS). *Two essential end hormones, cortisol, and epinephrine, regulate metabolism, circulation, and blood homeostasis.*

Abbreviations of hormones and neurotransmitters:

- *Hypothalamic hormones: CRH, corticotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; dopamine.*
- *Pituitary hormones: ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; Oxt, oxytocin; PRL, prolactin; TSH, thyroid-stimulating hormone.*
- *Adrenal cortex hormones: steroid hormones - corticosteroids (cortisol), mineralocorticoids, androgens,*
- *Adrenal hormone: E, epinephrine.*
- *Pineal gland hormone: melatonin.*
- *Other peripheral hormones are testosterone, T; estrogens, Es; thyroxin, T4; triiodothyronine, T3. somatomedins, IGF; angiotensin II; erythropoietin; calcitriol; somatostatin; glucagon; insulin; parathyroid hormone; calcitonin.*
- *Neurotransmitters: Neuropeptide Y, substance P, GABA, serotonin, dopamine, acetylcholine, norepinephrine, epinephrine.*
- *The authors' original drawing*


STRESS
Neurous system
Endorine system
Immune system
Cardiovascular system
Detoxifying system
Neurolia cells
Neurons
Hypothalamus
Pituitary
Adrenals
Thymus
Bone marrow
Blood cells
Blood vessels
Liver
Kidney
Gastro-intestine
Extracellular space
Hormones (CRH, ACTH, cortisol, GRH, BNDF, etc.), neurotransmitters, other ligands
Receptors
GPCR
tyrosine kinase receptor
toll-like receptor
AC
PLC
PI3K
ERK
MAPK
cAMP
BNDF
DAG
PKA
PKB/AKT
JNK
p38
PKC
NFk-B
Nrf-2
GSK3
AP-1/FOS
Gene regulatory proteins:
transcription and nuclear factors
Nuclear membrane
CREB

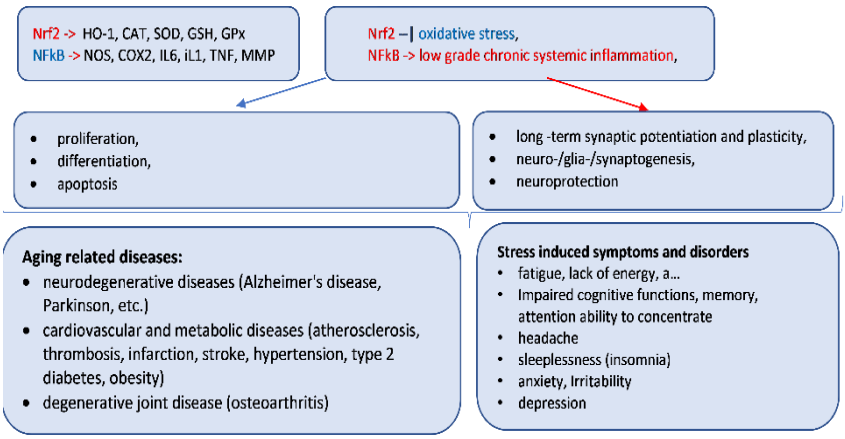


Fig. 6. Network pharmacology of GMT and acteoside: the hypothetic molecular mechanisms and modes of the pharmacological action of adaptogens; update from the authors' free access publications (Panossian and Efferth, 2022) and authors' drawings. Effects of adaptogens on key mediators of neuro-endocrine immune complex, cardiovascular and detoxifying systems that regulate adaptive stress response to stressors/pathogens in stress and aging-induced diseases and disorders. CRH- and ACTH-induced stimulation of GPCR receptors activates the cAMP-dependent protein kinase (PKA) signaling pathway in the regulation of energy balance and metabolism across multiple systems, including adipose tissue (lipolysis), liver (gluconeogenesis, glucose tolerance), pancreases, and gut (insulin exocytosis and sensitivity), etc. The key molecules involved in the PI3K-Akt signaling pathway are receptor tyrosine kinase (RTKs). Activating the PI3K-Akt signaling pathway promotes cell proliferation and growth, stimulates cell cycle vascular remodeling, and cell survival, and inhibits cell apoptosis in response to extracellular signals. The nonspecific antiviral action of ginseng is associated with the activation of innate immunity by upregulation of the expression of the pathogen's pattern recognition receptors, specifically toll-like receptors TLR-mediated signaling pathways. The protein kinase C (PKC) family of enzymes with isoforms plays an essential cell-type-specific role, particularly in the immune system, through phosphorylation of CARD-CC family proteins and subsequent NF-B activation.
Three stress-activated MAPK signaling pathways playing crucial roles in cell proliferation, differentiation, survival, and death have been implicated in the pathogenesis of many human diseases, including Alzheimer's disease, Parkinson's disease, and cancer. (1) The stress factors inducing the activation of the c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK) mediated adaptive signaling pathway are heat shock, irradiation, reactive oxygen species, cytotoxic drugs, inflammatory cytokines, hormones, growth factors, and other stresses. The activation of the JNK/MAPK10 signaling pathway promotes cell death and apoptosis via the upregulation of pro-apoptotic genes. (2) The activation of the extracellular-signal-regulated kinase (ERK) pathway is initiated by hormones and stresses to trigger endothelial cell proliferation during angiogenesis, T cell activation, long-term potentiation in hippocampal neurons, phosphorylation of the transcription factor p53, activation of phospholipase A2 in mast cells, followed by activation of biosynthesis leukotrienes and inflammation/allergy, etc. (3) The third major stress-activated p38 signaling pathway contributes to the control of inflammation, the release of cytokines by macrophages and neutrophils, apoptosis, cell differentiation, and cell cycle regulation. Activation is shown in red, while the inhibition is in blue color cycles/ellipses (effect of ginseng/ginsenosides), arrows, and clouds. BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CREB, cAMP-responsive element-binding protein; ERK, extracellular signal-regulated kinase; GSK-3glycogen synthase kinase-3; JNK; the c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK MAPK, mitogen-activated protein kinase; NF-B, nuclear factor-kappa B; Nrf2, nuclear factor E2-related factor 2; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKB, protein kinase B; PLC, phospholipase C.

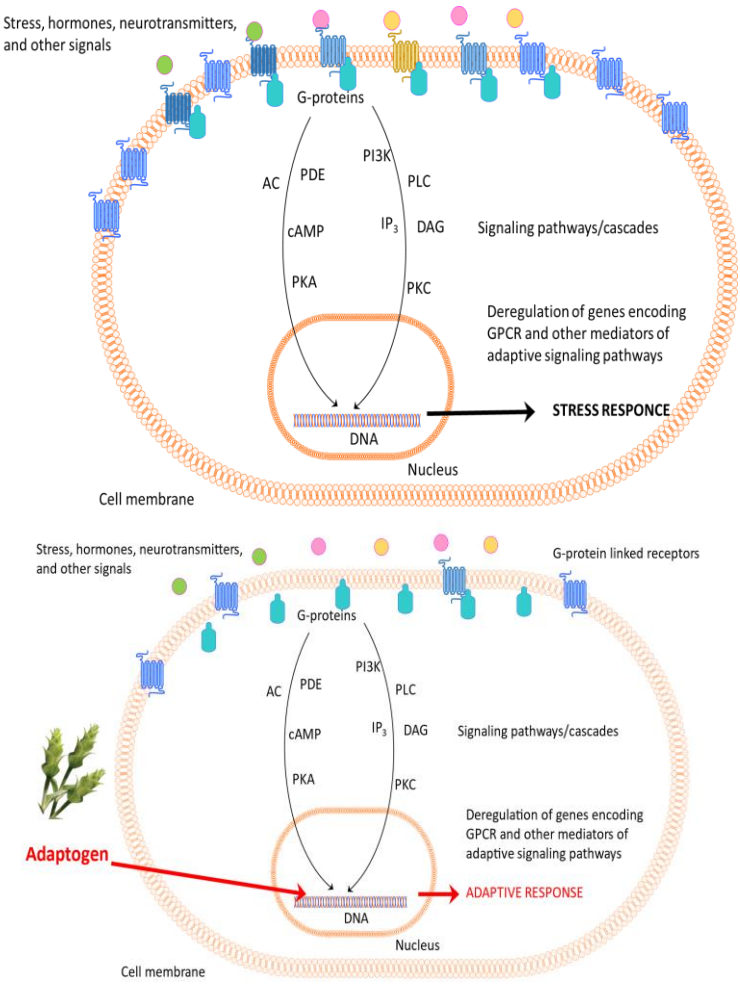


Fig. 7. The hypothetic mode of action of adaptogens triggers and mediates adaptive stress response by deregulating the expression of G-proteins. Adaptogens deregulate encoding GPCR and key mediators of GPCR signaling pathways. The lower panel shows down-regulation of GPCR when a cell is overstimulated by a neurotransmitter, hormone, or drug for a prolonged period, and the receptor protein's expression is decreased to protect the cell and reestablish homeostasis. Up-regulation occurs when a cell is deficient in some receptor. In this case, more receptor protein is synthesized and transported to the cell's membrane, and thus, the cell's sensitivity is increased back to normal, reestablishing homeostasis.

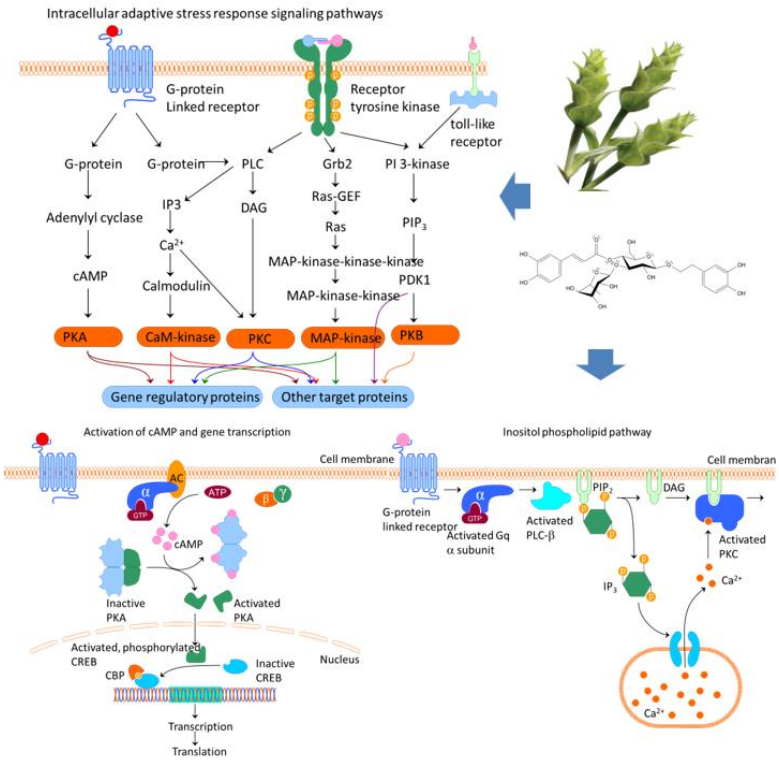


Fig. 8. The hypothetic molecular mechanisms and modes of GMT and acteoside on intracellular adaptive stress response signaling pathways, including on activation of cAMP and gene transcription, and inositol phospholipid pathways

6. The health-promoting features of AC are likely due to involvement in many adaptive canonical signaling pathways, such as MAPK, NF-κB, PI3K/AKT, TGFβ/Smad, and AMPK/mTOR (Xiao et al., 2022), Figs. 6-8.
7. A recent systematic review summarizing the studies of pharmacological mechanisms of antidepressant activity of acteoside uncovered the various pharmacological mechanisms, including (i) - modulation of monoamine neurotransmission, (ii) - inhibition of the hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis, (iii) - promoting of neuroprotection by inhibiting apoptosis, inhibiting ER stress, maintaining Ca 2+ homeostasis, up-regulating autophagy, and (iv) – suppression of oxidative stress and activation of innate antioxidant defense system (Zhao et al., 2023; Panossian, 2023).

It should be emphasized that GMT extracts, like any herbal extract, consist of many chemical compounds that interact both in a synergistic and antagonistic manner, suggesting that the effects of purified compounds 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 and Efferth, 2022; Panossian et al., 2015; Panossian et al., 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 to stress" with "multitarget effects on the neuroendocrine-immune system including:*

(i) *Triggering extracellular and intracellular adaptive signaling pathways* (Figs., 6,7) *that promote cell survival and organismal resilience in stress (Panossian et al. 2018),*
(ii) *Regulation of metabolism and homeostasis via effects on expression of stress hormones (corticotropin and gonadotropin-releasing hormones, urocortin, cortisol, neuropeptide Y, heat shock proteins Hsp70) and their receptors" (Panossian et al. 2018), and "indicated for use in stress-induced fatigue, mental and behavioral disorders, and aging-associated diseases*" (Panossian, 2017; Panossian, 2013; Panossian, 2023).

The recent findings supported by preclinical and clinical data suggest using *Sideritis scardica* extracts to improve cognitive functions and reduce the risk of age-related cognitive decline and neurodegenerative disorders.

Further clinical trials and some pharmacognostic characteristics are worthy of implementing national monographs on Herba Sideritis.

13. CONCLUSIONS

Greek Mountain Tea has been used for millennia. Current human trials confirm that GMT, administered at 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 oxygen to 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 working memory, improves reaction time, reduces anxiety, and improves mood. These major findings from a collaboration of British and German researchers concluded that polyphenols ferulic, chlorogenic acid and flavonoid apigenin likely cause these benefits. A German review of more than 4,000 studies on healthy elderly human subjects concluded that specific polyphenols, including those found in GMT, cross the blood-brain barrier, significantly improving information processing speed, executive function, and neuron function while reducing inflammation and free radical oxygen damage in the brain. In addition, a joint German-Norwegian study published in 2016 confirmed that highly enhanced cognitive function in elderly lab animals given

GMT concludes it “might be a potent, well-tolerated option for treating symptoms of cognitive impairment in the elderly…” “Well-tolerated” is a crucial concept here. No severe side effects have been attributable to GMT, even long-term use, as is common among rural people in Greece and surrounding countries.

A part of this monograph has focused on GMT's adaptogenic activity, which is a multitasker that provides the body with what it needs to increase resistance, resilience, and survival, playing a similar role in defending the plant against environmental challenges, including viruses, harmful bacteria, insect-borne diseases, excessive UV rays, environmental challenges, and the physiological ravages of chronic stress.

This monograph provides extensive knowledge and essential references for assessments of Herba Sideritis preparations' safety, efficacy, and quality to support drug regulatory bodies developing international or regional monographs on medicinal plants or national formularies on evidence-based and traditional herbal medicines. It includes details of botanical descriptions, chemical constituents, dosage recommendations, adverse effects, and interactions for health professionals, researchers, and policymakers, aiding in evidence-based practices and ensuring the safe use of medicinal products (Panossian, 2023). This monograph was primarily aimed to provide evidence supporting the indications of the use of GMT for treatments of diseases and not replace official compendia such as pharmacopeias, formularies, or legislative documents.

14. TERMINOLOGY

In this review, we use the commonly accepted terms and definitions below to avoid misuse of terminology, Table 2.

Table 2. Terminology and definitions

Terms	Definitions
Adaptogen	Adaptogens are botanicals that increase adaptability, resilience, resistance, and survival in stress and aging-related disorders. Adaptogens are characterized as botanicals with polyvalent action and pleiotropic activity. The term adaptogen is derived from adaptation, which is coned to the physiological process of adaptation of the organism to repeated action of the botanical that triggers adaptive stress response (hormesis) via intracellular and extracellular adaptive signaling pathways and networks in neuroendocrine-immune, cardiovascular, and gastrointestinal systems and resulting in increased adaptability, resilience, resistance, survival in stress-induced and aging-related disorders. Adaptogens play a similar role in defending the plant against environmental challenges, including viruses, harmful

Terms	Definitions
	bacteria, insect-borne diseases, excessive UV rays, environmental challenges, and the physiological ravages of chronic stress. Adaptogens exhibit stress-protective and tonic effects after repeated dose administration, triggering adaptive stress response signaling pathways and mediating gene expression in the HPA axis and other body tissues. The stimulating effects of a single dose of adaptogens are mainly due to neuro-talk within the CNS and HPA axis but do not require long-consuming processes such as gene and protein expression, neurogenesis, cell proliferation, and differentiation.
Affinity	Relating to the degree to which a substance tends to combine with another. Relating to chemical affinity depends on both stereochemistry and electrostatic interactions. Relating to electron affinity is the amount of energy released or spent when an electron is added to a neutral atom. Drug affinity is how well a certain drug can bind to a receptor.
Allosteric	Relating to the alteration of the activity of an enzyme through a conformational change induced by a different molecule An allosteric site is a site on a protein that is not the active site but can bind to an effector molecule and regulate the protein's activity.
Biased ligand	Biased ligands are those that can regulate receptor activity by stabilizing distinct conformations. Since the diverse signaling pathways elicit distinct physiological effects, biased ligands that selectively induce beneficial pathways hold promising therapeutic value. Ligand bias is the ability of ligands to activate specific receptor signaling responses compared with others differentially. It reflects differences in the responses of a receptor to specific ligands and has implications for the development of highly specific therapeutics.
Biased signaling	Biased signaling is a natural result of GPCR or allosteric function and should be expected from natural agonists or synthetic analogs. Biased signaling of G protein-coupled receptors or receptor tyrosine kinases describes the ability of different ligands that preferentially activate an alternative downstream signaling pathway.
Botanicals	Products that include plant materials, algae, macroscopic fungi, and combinations thereof A botanical drug product may be available as (but not

Terms	Definitions
	limited to) a solution (e.g., tea), powder, tablet, capsule, elixir, topical, or injection. Botanical drug products often have unique features, such as complex mixtures, lack of a distinct active ingredient, and substantial prior human use. Fermentation products and highly purified or chemically modified botanical substances are not considered botanical drug products.
Botanical hybrid preparations/products	The term botanical "Hybrid" preparation (BHP) is coined to describe the pharmacological activity (conditional pharmacological "signature") of a fixed herbal combination with a specific chemical composition (e.g., HPLC conditional chemical "fingerprint"), emphasizing that BHP exhibits unique biological characteristics and effects different from the ingredients' pharmacological characteristics.
Gene expression	Gene expression is the process by which information from a gene is used to synthesize a functional gene product - protein or RNA. Regulation of gene expression includes a wide range of mechanisms that cells use to increase or decrease the amount of corresponding gene products. Up-regulation is a process that occurs within a cell triggered by an internal or external signal, which results in increased expression of genes and corresponding proteins. Up-regulation occurs when a cell is deficient in some receptor. In this case, more receptor protein is synthesized and transported to the cell's membrane, and thus, the cell's sensitivity is increased back to normal, reestablishing homeostasis. Down-regulation is a process resulting in decreased gene and corresponding protein expression. Down-regulation occurs when a cell is overstimulated by a neurotransmitter, hormone, or drug for a prolonged period, and the receptor protein's expression is decreased to protect the cell and reestablish homeostasis.
Gene expression profiling	Gene expression profiling simultaneously measures the activity (expression) of 30,000 genes to create a global picture of cellular function.
Herbal substance	All are mainly whole, fragmented, or cut plants, plant parts, algae, fungi, and lichen in an unprocessed, usually dried form but sometimes fresh. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety, and author).

Terms	Definitions
Herbal preparations	are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration, or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices, and processed exudates.
Herbal medicinal products	Herbal medicinal products: any medicinal product exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.
Inflammation	A defense response of the body to harmful stimuli triggered by damage to living tissues. A set of complex changing responses to tissue injury primarily caused by toxic chemicals, some environmental agents, trauma, overuse, or infection. Some of these responses can be beneficial in wound healing and infection control or pathological as in many chronic disease states (Stone et al., 2022).
Inflammaging	A low-grade, aseptic, chronic inflammation developed with age, and is associated with age-related pathologies.
Ligand	In biochemistry, a ligand is any molecule or atom which binds reversibly to a protein.
Pharmacophore	The distinct functional groups or substance classes possess biological activity that is necessary to ensure optimal interaction features toward their receptor with a specific biological target structure and to trigger (or block) its biological response.
Pharmacodynamics	Pharmacodynamics refers to drugs' effects on the body, including receptor binding, post-receptor effects, and chemical interactions.
Pharmacokinetics	Pharmacokinetics describes how the body affects a drug's absorption, distribution, metabolism, and excretion of drugs in the organism after administration.
Pleiotropic action	The existence of drug effects other than the one for which the drug was explicitly implemented is usually implied by pleiotropy. In Pharmacognosy and ethnopharmacology, pleiotropy action refers to all actions of a botanical preparation other than those for which it was explicitly implemented. It is often used to denote additional beneficial effects but may have detrimental adverse effects. Pleiotropy is a term used in genetics to describe a single gene that controls or influences several

Terms	Definitions
	(potentially unrelated) phenotypic characteristics.
Polypharmacology	Polypharmacology refers to the binding of a drug to multiple target proteins, with clinical effects being mediated through the modulation of the set of protein targets.
Polyvalent action:	Polyvalence refers to a range of biological activities a botanical preparation may exhibit, contributing to the overall effect observed clinically or in vivo. Polyvalence can be due to the following: ○ Various types of phytochemicals are present, each type having a different biological effect. ○ Compounds of one particular phytochemical type have more than one biological effect relevant to treating the disease and improving the patient's health. ○ Compounds are present, which do not affect the cause or symptoms of the disease but modify the absorption, distribution, metabolism, and excretion of active constituents and the adverse effects.
Selective action	A drug strongly prefers its intended target over other targets, The degree to which a drug acts on a given site relative to others, The ability of a drug to affect a particular gene, protein, or signaling pathway in preference to others, A drug that binds to the same receptor as an agonist but produces an effect opposite to that of the agonist.
Specific action	An accurate, exact (free from ambiguity), distinctive influence peculiarly adapted to a purpose or use.
Synergistic action	The synergy refers to a combination of constituents' working together" when: ○ a positive effect is obtained but not expected with one of its constituents ○ an increase in the positive impact of a combination of substances is more significant than anticipated. Synergism is strictly concerned with only one pharmacological function rather than a range of activities resulting in an overall effect.
Systems pharmacology	It seeks to understand how drugs affect the human body as a single complex biological system. Instead of considering the effect of a drug to be the result of one specific drug-protein interaction, systems pharmacology refers to the impact of a drug to be the outcome of the network of interactions a drug may have. Interaction networks may include chemical-protein, protein-protein, genetic, signaling, and physiological (at cellular, tissue, organ, and whole-

Terms	Definitions
	body levels). Systems pharmacology uses bioinformatics and statistics techniques to integrate and interpret these networks.
Network pharmacology	Network pharmacology is a subfield combining principles from pharmacology, systems biology, and network analysis to study the complex interactions between drugs and targets (e.g., receptors or enzymes) in biological systems. The topology of a biochemical reaction network determines the shape of the drug dose-response curve and the type of drug-drug interactions, thus helping design efficient and safe therapeutic strategies. The topology Network pharmacology utilizes computational tools and network analysis algorithms to identify drug targets, predict drug-drug interactions, elucidate signaling pathways, and explore the polypharmacology of drugs.
Synergy	Two or more agents work together to produce a result not obtainable by any of the agents independently, which was interpreted as generating new pharmacological activity specific only to the combination of two or more agents. Another definition of synergy is broadly interpreted as *a combination of agents that is more effective than is expected from the effectiveness of its constituents* without specifying differences between potentiation and amplifications.
Systems biology	Systems biology deals with computational and mathematical analysis and modeling of complex biological systems. It is a biology-based interdisciplinary field that focuses on complex interactions within biological systems and uses a holistic approach to biological research.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

The author A.P. has no conflicts of interest to declare. Author A.P. is self-employed at the research and development company Phytomed AB and has no shares or financial interest in any pharmaceutical company. The author T.L. is the founder of EuropharmaUSA Inc., Green Bay, Wisconsin, USA.

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