The EuroBiotech Journal
REVIEW
EBTNA UTILITY GENE TEST
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Pharmacologically active fractions of *Sideritis* spp. and their use in inherited eye diseases

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Abstract

The main constituents of the genus *Sideritis* are various terpenoids, sterols, coumarins, flavonoid aglycones and glycosides. *Sideritis* species have been traditionally used as infusions or flavoring agents and in medicine as anti-inflammatory, antiulcer, antimicrobial, antioxidant, antispasmodic and analgesic agents. This paper includes the following sections: Introduction, Description and distribution of *Sideritis* spp, Pharmacological effects, Toxicity tests, Rationale for use of *Sideritis* spp. in ophthalmology and Conclusions. The aim is to provide a comprehensive overview on the botanical, phytochemical and pharmacological aspects of the genus *Sideritis*, and to establish the scientific basis of its pharmacological use. New approaches to using officinal plants have recently yielded significant results. The paper also reviews this information and provides a critical view on the options for exploiting the potential of *Sideritis* spp. in ophthalmology.

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Published online: 27 October 2017
doi:10.24190/ISSN2564-615X/2017/S1.02

Introduction

The use of plants and their extracts for therapeutic purposes dates back to ancient times and is the basis of many effective therapies (1). Plants are a source of a variety of natural compounds with different chemical structures and a broad range of biological activities. Plant biodiversity with its richness and complexity is the major source of chemical diversity (2). The most active agents that may apply to certain therapeutic areas are products of secondary metabolic pathways, the biological function of which is often self-defense against herbivores and various pathogens. Research in the field of biology, chemistry and medicine is directed at identifying and characterizing plant secondary metabolites with pharmacological activity that could be candidates for the synthesis of new drugs. The natural product database has a large number of unused scaffolds and the differences between synthetic and natural products are remarkable (2,3). Among officinal plants, the *Lamiaceae* family includes some extremely interesting examples that offer natural substances and high quality raw materials. The study of these species not only aims at the quantity of biomass produced but above all at specific efficient secondary metabolites. In this context, research into genetic variability and agronomic and phytochemical characteristics is important to pinpoint the most suitable biotypes for different sectors. In ophthalmology there is interest in treatment with officinal plants that unlike traditional drugs, do not contain synthetic compounds. Attention recently focused on *Sideritis* spp. for the treatment of hereditary eye diseases.

Description and distribution of *Sideritis* spp.

The genus *Sideritis*, belonging to the Lamiaceae family, includes herbaceous plants commonly known as "ironwort". Officinal species grow mainly in the Mediterranean especially in Spain, Italy, Albania, Bulgaria, Greece and Turkey, where 140 native species are known, divided into roughly 320 subspecies, ecotypes and cultivars (4). Hybridization be-

tween different species makes botanical classification difficult and changes the chemical concentration of pharmacologically active components. Several species are used in infusions to aid digestion, strengthen the immune system and to suppress flu, sinus congestion, allergies, even pain and mild anxiety. The Greek species, *Sideritis euboea* and *Sideritis scardica,* known as Greek mountain tea, have a long history in traditional Mediterranean medicine. The *Sideritis* genus is composed of annual and perennial herbaceous plants and small shrubs. These plants have a shaggy or downy layer of microscopic intertwined hairs. The inflorescence is composed of verticillasters. Leaves are often narrow, opposite, entire or crenate-dentate, sessile to petiolate. Calyx tubes are tubular-campanulate, and the corolla is mostly yellow, rarely white or red, and shorter than the calyx. *Sideritis* species grow optimally in full sun and are well suited to drought conditions. They are found on rocky slopes and pastures, from a few meters above sea level to altitudes of more than 3000 m, and require slightly alkaline, moderately nutrient rich soils (5,6). The plants richest in pharmacologically active substances grow to over 1000 m.

The genus has two subgenera, *Sideritis* and *Marrubiastrum,* defined by morphological, karyological, palinological and genetic aspects (7). Chromosomal studies show that all species of the genus *Sideritis* have 2n=32 isodiametric metacentric A chromosomes; the different phenotypes of the specie denote variance among the genes (8).

Only a few species are cultivated; they include *Sideritis sardica*, which is indigenous to Mt. Olympus (9). All species are known to be high in terpenes, flavonoids and essential oils, chemical components responsible for their pharmacological activity:

- **Terpenes:** Terpenes are a large class of organic hydrocarbons occurring widely in plants and animals. They are empirically regarded as being built up from isoprene, a hydrocarbon consisting of five carbon atoms attached to eight hydrogen atoms (C_5H_8). True terpenes are usually grouped according to the number of isoprene units in the molecule: monoterpenes ($C_{10}H_{16}$) contain two such units, sesquiterpenes ($C_{15}H_{24}$), three, diterpenes ($C_{20}H_{32}$), four, triterpenes ($C_{30}H_{48}$), six, and tetraterpenes ($C_{40}H_{64}$), eight. *Sideritis* species are rich in diterpenes: 160 different diterpenes have been isolated from the aerial parts (10). Kaurene diterpene derivatives (foliol, sidol, linearol, sideridiol and isolinearol), labdane (ribenol and andandalusol), beyerane (tobarrol and conchitriol), rosane (lagascatriol) and atisane (serradiol) are the most frequently found in *Sideritis* species. In Italy, Turkey and Greece there are species that contain almost exclusively kaurane diterpenes (11). Several biological activities have been reported for diterpenes, including anti-inflammatory, anti-bacterial, anti-fungal, anti-leishmanial, cytotoxic and anti-tumor (12).
- **Flavonoids:** Chemically, the flavonoids have the general structure of a 15-carbon skeleton, which consists of two phenyl rings and a heterocyclic ring. This carbon structure can be abbreviated C_6-C_3-C_6. According to IUPAC nomenclature, they can be classified as: flavonoids or bioflavonoids, isoflavonoids, derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structure, and neoflavonoids, derived from 4-phenylcoumarine (4-phenyl-1,2-benzopyrone) structure. 5,6,7-trioxygenated flavones (cirsimaritin, salvigenin and nepetin) are predominant in *Macaronesian* species, whereas 5,6,7,8-tetraoxygenated flavones (sideritoflavone, xanthomicrol and gardenin-B) are predominant in Mediterranean species. Differences in flavonoid composition have also been used to distinguish two of the sections into which the *Sideritis* genus is classified (13). Flavonoid aglycones are the most frequent and include sideritoflavone, chrysoeriol and xanthomicrol. Other major flavonoids identified are luteolin-based and apigenin-based derivatives (9,14).
- **Several natural products**, showing anti-inflammatory, antioxidant and anti-ulcerogenic activities that have been isolated from plants of this genus, mainly include flavonoids (15). It was recently discovered that flavonoids from *Sideritis* species are selective inhibitors of monoamine oxidases (MAOs); these flavoenzymes located in the outer membrane of the mitochondria have an important role in the oxidative catabolism of amines. Flavonoids are therefore potential natural molecules for developing novel selective MAO inhibitors for the treatment of psychiatric disorders such as depression and anxiety, as well as cognitive impairment in Alzheimer's and Parkinson's diseases (16).
- **Essential oil:** An essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants. Essential oils are also known as volatile oils, ethereal oils, aetherolea, or simply as the oil of the plant. *Sideritis* species have been reported to be poor in essential oils. Differences in essential oil components from the same species may be due to climatic and genetic factors, horticultural practices, plant chemotype and nutritional status (17). Essential oils have antimicrobial activity. The major essential oils are monoterpene hydrocarbons, including alpha-pinene, beta-pinene, beta-phellandrene, sabinene and myrcene; oxygenated sesquiterpenes, such as thymol, have been found in some species in Greece (18).

Pharmacological effects

Sideritis species are important in the treatment of various types of disorder; infusions and decoctions are prepared from aerial parts and administered orally and topically.

Sideritis species have been used popularly for centuries for their anti-inflammatory, anti-ulcerogenic and antimicrobial properties (19,20). The main clinically useful activities of *Sideritis* species have been well studied:

- **Anti-inflammatory activity:** Different extracts and fractions obtained from the aerial parts have been examined. Many studies have focused on the anti-inflammatory activity of isolated diterpenoids from *Sideritis* species. They have significant anti-inflammatory activity in the second stage of inflammation (21).

Pharmacological effects are due to diterpenes, including serradiol, linearol, conchitriol, foliol, isofoliol, andalusol, lagascatriol, tobarrol, sidol and siderol, identified by reverse-phase chromatography (9,14). The best way to extract active ingredients is using a 70/30 water/ethanol solution as mobile phase. Concentrations of active ingredients differ significantly between species.

Anti-inflammatory activity has been studied in isolated flavonoids. Flavonoids with hydroxyl substituents in their structure, except for the B-ring, are selective against cyclo-oxygenase enzyme activity (22).

Infusions (4%) of *Sideritis clandestina* administered to mice for 6 weeks at two doses showed a positive effect on visual-spatial memory. A second study on mice with Alzheimer disease showed a 55% reduction in alpha amyloid deposition in the brain (9,23).

The plant has been studied for an anti-inflammatory effect on chemically induced corneal edema. Oral administration of 30 to 60 mg/kg of the sterol fraction inhibited edema with a peak 3 hours after infusion (18).

Foliol and linearol have anti-inflammatory activity, inhibiting expression of NOS-2 and COX-2 elicited by LPS-induced macrophage activation. The pharmacological effect of foliol and linearol occurred at concentrations between 5 and 10 µmol. When the study was extended to investigate cytotoxic effects, no toxic effect was found in the 5-10 µmol concentration range (9,18).

- **Antimicrobial activity:** *Sideritis* species have documented antimicrobial activity: some species inhibit Gram-positive and others Gram-negative bacteria. For example, ethanol extracts of *Sideritis leptoclada* and *Sideritis albiflora* are only active against Gram-positive bacteria (24), whereas methanol extract and butanol and chloroform fractions from *Sideritis albiflora* and *Sideritis brevibracteata* and the methanol extract and chloroform fraction from *Sideritis pisidica* may be active against both Gram-positive and Gram-negative bacteria (25). Methanol extracts of several Turkish *Sideritis* species (above all *Sideritis bilgerana and Sideritis trojana*) exhibit antimycotic activity against clotrimazole-resistant *Candida albicans* (26). Antimicrobial activity of several isolated diterpenoids has also been reported; in particular, foliol and isopusillatriol are significantly active against Gram-positive bacteria and acid-fast bacteria (27).
- **Antioxidant activity:** *Sideritis* species have proven antioxidant activity (28). There is a correlation between phenol content and antioxidant capacity (29). Antioxidant effects have been studied in PC12 cells subjected to oxidative stress with H_2O_2 (9,18).
- **Analgesic activity:** The ethanol extract and chloroform fraction of *Sideritis lotsyi* have anti-nociceptive effects. An oral dose of 400 mg/kg of petroleum ether extract from *Sideritis taurica* has an analgesic activity similar to that of 400 mg/kg acetylsalicylic acid at 45 and 60 min (30).
- **Anti-ulcerogenic activity:** The in vivo anti-ulcerogenic activity of *Sideritis* species is well known. Hypolaetin-8-O-α-d-glucoside, a flavonoid present in several *Sideritis* species, reduces gastric lesions and ulcers in rats (31). Decoctions prepared from aerial parts of *Sideritis caesarea* have a gastroprotective effect against ethanol-induced gastric ulcer in rats (32). *Sideritis italica* essential oil also has strong activity against *Helicobacter pylori* (33). These findings confirm the traditional gastroprotective use of *Sideritis* species.
- **Antitumor activity:** Methanol extract from *Sideritis libanotica* ssp. linearis is reported to have anti-proliferative activity against three human cell lines: C6 cells, Vero cells and HeLa cells (34). *Sideritis* aqueous extracts have selective estrogen receptor modulator activity: indeed *Sideritis euboea* and *Sideritis clandestina* induce osteoblast differentiation of KS483 cells and suppress breast cancer cell growth (35).
- **Antiviral activity:** Study of the anti-HIV activity of these plants showed that 26 semisynthetic derivatives of linearol inhibit virus replication (36). The dichloromethane extract showed antiviral activity against herpes simplex viruses, an important result in view of the emergence of drug-resistant (e.g. acyclovir-resistant) HSV mutants (37).

Toxicity tests

Since studies on the toxicity of sideritis extract have not detected any substantial effect, category 5 toxicity (LD50 = 2000-5000 mg/kg body weight) has been assigned. Chronic intake toxicity was tested on mice that took the extract for 28 days; a toxic effect on white blood cell count was only detected at a dose of 500 mg/kg. Genotoxicity tests did not detect any risk. Four *Sideritis scardica* dry extracts of different polarity (water, 20% and 50% V/V ethanol, and n-heptane) were tested (AMES-test in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 102 with and without metabolic activation). No signs of genotoxicity or mutagenicity were observed.

No cases of overdose have been reported and no data is available on modified reflexes for car driving or attention. Use in children and adolescents under 18 years of age is not recommended due to lack of data. Its use is likewise not recommended during pregnancy and lactation, as its safety has not been tested under these conditions. Tests on carcinogenicity and reproductive toxicity have not been performed (9).

Rationale for the use of *Sideritis* spp. in ophthalmology

Approximately 200 plants worldwide have been documented to have ophthalmic effects that support treatment of eye disorders (38). Specific understanding of eye anatomy and biochemistry are necessary to treat eye diseases with plants. The fact that very specific plants soothe eye inflammation is interesting, because it indicates that certain plants have an affinity for eye tissues.

There is an ophthalmological tradition of treating the eyes with officinal plants, which includes *Sideritis* species for their

anti-inflammatory activity. Inflammation may become a pathological process, causing tissue damage and impairing visual function. Corticosteroid-based treatments have been associated with secondary effects, including glaucoma and posterior subcapsular cataract (39,40): hence the interest in finding effective natural substances without side-effects for treating eye inflammation. The topical anti-inflammatory activity of aqueous and hexane extracts of *Sideritis javalambrensis* has been found to suppress corneal edema. Both plant preparations showed anti-inflammatory activity during the chronic and intermediate stages of inflammation when edema was most intense; the hexane extract exerted a protective effect (41).

Our studies show that titrated extract of pharmacologically active substances obtained from two fractions of the plant (pharmacologically active ironwort fractions) is effective in degenerative diseases of the retina and optic nerve and in inflammatory diseases of the cornea. Its effect on retinal degenerative diseases and glaucoma is presumably due to inhibition of microglial activation, whereas its effect on corneal dystrophy and keratoconus is due to anti-inflammatory activity.

Conclusions

Various studies explain the basis of traditional medical uses of *Sideritis* species and sustain motivation to find new pharmacological effects. Species of the genus *Sideritis* are rich in diterpenoids, flavonoids and essential oils. Various pharmacological studies show that these components have antimicrobial, anti-inflammatory, anti-ulcer, analgesic, antiviral, anti-tumor and antioxidant activities. Through innovative biotechnologies, medicinal plants already offer great opportunities and solutions in medicine. The management of eye disorders and diseases by drugs without side-effects is still a challenge. Herbal medicines have the potential to overcome the limitations associated with conventional drugs. Modern techniques and polymers should enable the best natural formulations to be developed. Past research already proves that herbs really have benefits for eyes. Future research should focus on the pharmacological activity of compounds isolated from *Sideritis* species in order to find new active principles for ophthalmology.

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