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Sideritis species in challenging against cancer: Cytotoxic, antiproliferative and apoptotic roles on different cancer cells

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Abstract: *Sideritis* species belonging to Lamiaceae are represented by many species worldwide. They exhibit many bioactivities including antioxidant, anticancer, antimicrobial, anti-inflammatory due to their important phytochemicals. Moreover, they are thought to be important resources in the fight against cancer, especially due to their cytotoxic effects on cancer cells. Many studies on various cancer cells have reported cytotoxic, antiproliferative and apoptotic properties of *Sideritis* species. In this study, the phytochemical contents of *Sideritis* species growing in different geographies and their cytotoxic, antiproliferative and apoptotic effects in the fight against cancer were discussed in detail.

Keywords: *Sideritis*, anticancer, antiproliferation, apoptosis, bioactivity

1. Introduction

Cancer is among the diseases that cause the death of many people today. Factors such as smoking, an unhealthy diet, high alcohol consumption, physical inactivity, and excess body weight are among the main factors in the emergence of cancer (Islami et al. 2018). According to research conducted in recent years, lung cancer ranks first among the most common types of cancer, although the order may vary between men and women. However, cancer types such as breast, prostate, colon, cervix and thyroid are also quite common. (Siegel et al. 2023). Many patients diagnosed with cancer die and it is thought that these deaths will increase in the future.

There are different methods in the treatment of cancer such as chemotherapy, radiotherapy, immunotherapy and surgery (Huang et al. 2017). There are compounds of synthetic and natural origin used in chemotherapy. However, especially synthetic-based chemicals can cause side effects such as anaphylaxis, cytopenias (including leukopenia and neutropenia, thrombocytopenia, and anaemia), hepatotoxicity, ototoxicity, cardiotoxicity, nausea and vomiting, diarrhea, mucositis, stomatitis, pain, alopecia, anorexia, cachexia, and asthenia (Oun et al. 2018). Therefore, many studies have focused on compounds with fewer side effects isolated from natural sources such as plants. Agents such as vincristine, vinblastine, vindesine, vinorelbine (Vinca Alkaloids), paclitaxel and docetaxel (Taxanes) and epothilones are some of plant-deriveted agents used in the chemotherapy treatment of cancer (Marzo and Naval 2013). Paclitaxel (taxol) is a compound isolated from *Taxus brevifolia* and is used clinically for the treatment of cancer (Karuppusamy and Pullaiah 2022). The number of chemicals isolated from plants such as taxol is increasing but still remains insufficient.

There are reports in studies conducted with members of many plant families showing the interactions of these plants with cancer cells. Plant extracts and compounds have been shown to suppress events such as cell proliferation, invasion and metastasis by activating the cell death pathway and break acquired drug resistance (Ege et al. 2020; Cocelli et al. 2021, Yumrutas and Yumrutas, 2022, Yumrutas and Bozgeyik, 2023). Anticancer studies using plants generally focus on compounds such as alkaloids, terpenoids and phenolics isolated from them (Jiang and Hu, 2009; Rabi and Bishayee 2009; Carocho and Ferreira 2013). One of the most well-known plant families screened for these substances is Lamiaceae. It is represented by many species around the world, and species belonging to this family have been used since ancient times. The sage is among the most well-known in this family and also many species are also consumed as spices and tea. Among these species, *Sideritis*, which has many chemical compounds and has high pharmacological effects due to these compounds, is quite remarkable. *Sideritis* genus, known as "mountain tea" in Turkey, has important ethnobotanical characteristics. Compounds such as phenolic and terpenoid contained in it play a role in exhibiting important biological activities, especially antioxidant. In this review, the distribution of *Sideritis* species, their genus characteristics, their pharmacologically valuable phytochemicals, their bioactivities and especially their possible effects on cancer cells are discussed in detail.

2. Characteristics of *Sideritis* species

From past to present, people have used plants for nutrition, shelter, warmth, healing their wounds and treating their diseases. It has been determined that there were 250 plants that people used in treatments in 5000 BC. Hittites, Egyptians, Sumerians, Assyrians and Mesopotamians have used plants for treatment for years. Over time, the use of synthetic drugs has led to a decrease in the use of medicinal aromatic plants. After the 1900s, it has discovered the side effects of synthetic drugs, and therefore the demand for natural products has increased (Göktaş and Gıdık 2019). With developing of modern science, it has been shown that the phytotherapeutic effects of plants are related to biologically active compounds formed through secondary metabolites (Kralova and Jampilek 2021). Medicinal plants, which have economic and medicinal value, are gaining increasing importance and providing increasing benefits to people (Chen et al. 2016).

It has been reported that the medical plants have been used in treatment of diseases including cardiovascular diseases, endocrine system disorders such as diabetes and goiter, prostate, kidney and urinary tract inflammations, lung diseases such as bronchitis, asthma and breath-opening, in upper respiratory tract diseases such as flu, cold, sore throat and cough, in stomach problems such as reflux, ulcers and gastritis, in intestinal diseases such as abdominal pain, constipation and diarrhea, in dermatological disorders, joint pains, arthritis, muscle and joint diseases such as rheumatism, Alzheimer's disease (AD), Parkinson's disease (PD) and cancer (Baytop 1999; Karousou and Deirmentzoglou 2011; Arıtuluk and Ezer 2012; Chiarini et al. 2013; Ozturk et al. 2013; Melikoğlu et al. 2015; Gregory et al. 2021; Yin et al. 2021).

Moreover, in recent years, there has been a global trend towards the use of natural substances. Plants as a source of antioxidants and functional ingredients are used by the food industry to adapt to the consumer market (Dziki et al. 2014). According to available statistics, medicinal plants have attracted more and more attention in recent years. While the market share of medicinal plants in developing countries is increasing, it is high in developed western countries such as Europe (He et al. 2018) In traditional and ethnomedicine, medicinal plants have long been recognized as the basis of materials used in therapeutic practices worldwide. The remarkable healing effect of traditional Chinese medicine using herbal mixtures, especially during the Corona Virus Disease 2019 (COVID-19) epidemic, has attracted great attention worldwide (Zhang and Wang 2023). Lamiaceae is one of the most important families containing a wide variety of plants with biological and medicinal applications (Uritu et al. 2018). It consists of approximately 245 genera and 7886 species. They are distributed almost all over the world, except for the cold polar regions (Abdelhalim and Hanrahan, 2021). Some of these plants and their secondary metabolites are highly appreciated in the food, agricultural, cosmetic and pharmacological industries (Trivellini et al. 2016). Some of the largest genuses are *Salvia* (900), *Scutellaria* (360), *Stachys* (300), *Plectranthus* (300), *Hyptis* (280), *Thymus* (220) and *Nepeta* (200). Many of these plants are used as spices and vegetables (Tamokou et al. 2017).

The Lamiaceae species are distributed almost all over the world, especially in tropical and temperate regions. The Lamiaceae is known for its numerous species with medicinal properties and has a high content of essential oils, polyphenolic compounds, and terpenoids with important biological activities. Numerous studies have been reported on different species of the Lamiaceae and their effects on memory, anxiety, depression and sleep disorders (Abdelhalim and Hanrahan 2021).

Although the *Sideritis* genus is distributed throughout the world, especially in the Mediterranean basin, it is represented by more than 150 species in a wide area from the Bahamas to China, from Germany to Morocco (Öke 2006).

The therapeutic use of *Sideritis* species was first mentioned in Dioscorides' book written in the 1st century; Mentioned in "*De Materia Medica*". The genus *Sideritis* L. takes its name from the Greek word "sideros" (iron) and has been used since ancient times to heal wounds caused by weapons such as swords. Folklorically, decoction or infusion prepared with the aerial parts of *Sideritis* species has been used orally or topically for centuries due to its anti-inflammatory, antiulcerogenic, digestive, antispasmodic, anticonvulsant, antimicrobial, analgesic and wound healing properties (Gonzales-Burgos et al. 2011; Yeşilada et al. 1995).

One of the two main gene centers of *Sideritis* genus is Turkey and therefore the endemism rate is 79.5%. Many medicinal properties have been determined in the extracts obtained from *Sideritis* species, and it is known that interest in the plant has increased due to these properties. In particular, its antistress, antibacterial, insecticidal, antiulcer, analgesic and anti-inflammatory effects have been detected. It attracts special attention due to its antioxidant properties (Arabacı et al. 2014).

3. Overview of biological activities of *Sideritis* species

When the biological activities of *Sideritis* species are evaluated, the first thing that stands out is their strong antioxidant activity. It is thought that the strong phenolic compounds found in its structure are responsible for these activities. In the studies conducted, they exhibited significant activities especially in tests such as DDPH, ABTS and power reducing. Erkan et al. (2011) reported that *S. congesta* and *S. arguta* species showed strong DPPH and ABTS free radical scavenging activities due to their important cinnamic acid and flavonoid derivatives. In a different study, *S. raeseri spp. raeseri* has been shown to reduce the arterial pressure and heart rate at doses of 24.31±3.87 mg/kg and 88.14±7.51 mg/kg (EC_{50}). (Kitic et al. 2012). Additionally, in the same study, *S. raeseri* (0.005-1.5 mg/ml) showed a vasodilator effect in aortic preparations and caused a decrease in chronotropic and inotropic activity in rat atria. Goulas at al. (2014) reported that the extract obtained from *S. syriaca* by the decoction method showed a remarkable antimicrobial activity against Staphylococcus aureus. It was determined that *S. scardica* methanol extract significantly reduced total tau, activation of GSK3, ERK1 and/or ERK2 kinases of tau, as well as tau hyperphosphorylation in the in vitro Alzheimer's test model with SH-SY5Y and PC12 cells (Chalatsa et al. 2018). In another study (Ververis et al. 2023), it was shown that diethylether, ethylacetate and butanol fractions of *S. scardica*, which were determined to be very rich in phenolics, protected the viability of Aβ25–35-treated SH-SY5Y human neuroblastoma cells. In a different study, anti-aging activity of *S. scardica* was demonstrated through collagenase inhibition, prevention of advanced glycation end product (AGE) formation, antioxidative and antiallergic activities, and ultraviolet B (UVB)-induced matrix metalloproteinase-1 (MMP-1) expression inhibition (Sato et al.2022). Hernandez-Perez et al. (2002) showed that *S. lotsyi* var *mascaensis* ethanol and chloroform fractions had a significant topical anti-inflammatory and analgesic effect in carrageenan and 12-o-tetradecanoyl-phorbol-acetate-induced paw and ear oedema and in an acetic acid-induced pain model in mice. In another study, acetone extract of *S. condensanta* exhibited insecticidal/acaricidal activity against *Bemicia tabaci*, *Lasioderma serricorne* and *Sitophilus granarius*, while linearol isolated from *Sideritis* condensanta exhibited activity against *Bemicia tabaci*, *Lasioderma serricorne*, *Tetranychus urticae* (Kilic et al. 2009). Deveci et al. (2019) reported that while the urease and choline esterase (AChE and BChe) inhibitory activities were detected in hexane, acetone and methanol extracts of *S. albiflora*, tysinase inhibitory activity was shown only in acetone and methanol extracts. Küpeli et al (2007) reported that *S. ozturkii* acetone extract and ozturkoside C showed strong antinociceptive activity in the p-Benzoquinone-induced abdominal constriction test and a strong anti-inflammatory effect in the Carrageenan-induced hind paw edema model. Although the biological activities of some *Sideritis* species have been mentioned above, other information for comparison is given in Table

4. Cytotoxic and antiproliferative effects of *Sideritis* species against cancer cells

The first method used to determine the anticancer activities of an extract or compound is usually cytotoxicity tests. In these tests, cells are grown in vitro and then exposed to the agent used. Finally, the cells are stained with chemicals such as MTT (3- (4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide), SRB (sulforhodamine B), XTT ((2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide), BrdU (Bromodeoxyuridine) and the cells are measured spectrophotometrically to measure cell viability and proliferation. There are many studies showing the cytotoxic activity of extracts and compounds obtained from medicinal plants on cancer cells. Among these plants, *Sideritis* genus has great importance. Previous studies have shown the cytotoxic effects of *Sideritis* species growing in different geographies on different cancer cells. In the light of the data obtained in the studies, it can be said that *Sideritis* species can significantly inhibit the survival and proliferation of cancer cells. Table 2 shows information about the possible cytotoxic effects of *Sideritis* species on cancer cells.

5. Apoptotic effects of *Sideritis* species against cancer cells

It has been reported in the above studies that the viability and proliferation of cancer cells are significantly reduced by extracts and agents obtained from *Sideritis* species. Although an extract or compound has an antiproliferative and cytotoxic effect, it is not sufficient to evaluate anticancer activity by cytotoxic activity alone. Some of the main reasons for this are that cells can also die from factors other than the extract applied under in vitro conditions. Among these, cells may die spontaneously due to stress conditions such as the high number of passages, storage conditions, quality and content of the media used, sensitivity of the researcher, infection of the cells, and errors that may occur in the devices used in cell incubation. Therefore, it is necessary to use some molecular markers in addition to the cytotoxic effects of an extract or compound whose anticancer activity is tested. One of the most used tests for this is AnnexinV and propodium iodide (alternative stains such as 7ADD are used). The basic principles here are to stain phosphotidylserine, which moves from the cell's inner membrane to its outer membrane when a cell undergoes apoptosis, with fluorescent agents and to determine the rate of apoptosis with cell counting devices or fluorescent microscopes (Van Engeland et al. 1998).

Apoptosis is one of many known death pathways and is a programmed death pathway (Savitskaya and Onishchenko, 2015). Under normal conditions, cells divide, differentiate and die throughout their lives. Apoptosis plays an important role in this process. Irregularities in apoptosis may cause important diseases, especially cancer. Cells that enter the cancer pathway continue to survive by suppressing this pathway and escaping the immune system. As a result, during apoptosis, swelling of the cell membrane, condensation of chromosomes, fragmentation of DNA and small vesicles of the cell membrane, cytoplasm and organelles are observed in late apoptosis (Poon et al. 2014). Apoptosis, which can be grouped as intrinsic and extrinsic, is controlled by important enzymes. Both apoptotic and anti-apoptotic proteins play a role in both apoptotic pathways. Depending on the levels of these proteins, the relevant apoptotic pathway is activated in the cells. Apoptotic proteins such as Bax, Noxa, and Puma serve as proteins that initiate apoptosis. Proteins such as Bcl-2, Mcl1, Bcl-xl are found in the mitochondrial membrane and suppress mitochondrial apoptosis.

Table 1. Overview to the biological activities and phytochemicals of *Sideritis* species

No	Species	Activities	Extracts	Compounds	References
1	*Sideritis brevibracteata*	DPPH free radical scavenging activity, reducing power (CUPRAC) assay, β-carotene antioxidant tests, no anticholinesterase activity, weak butyryl-cholinesterase activity	Acetone, methanol, essential oil	Caryophyllene, germacrene-D, and α-cadinene, quercetagetin-3,6-dimethylether and chlorogenic acid, siderol, linearol, eubotriol, 7-acetyl sideroxol	Sagir et al. 2017
2	*Sideritis sipylea*	DPPH free radical scavenging activity, tyrosinase and elastase inhibitory activity	Methanol, ethyl acetate, acetone, dichloromethane, essential oil	α-pinene, β-pinene, sabinene, verbenol, and borneol, β-caryophyllene and caryophyllene oxide, geranyl linalool, Siderol, sideridiol, and 7-epicandicandiol, echinacoside, forsythoside B, verbascoside,samioside,isoverbascoside, allysonoside, and leucoseptosideA,4-O-methylisoscutellarein 7-O-allosyl- (1→2)-[6"-O-acetyl]-glucoside	Axiotis et al. 2020
3	*Sideritis congesta*	DPPH free radical scavenging and ABTS free radical scavenging activities	Acid hydrolysis of methanol, ethyl acetate, acetone extracts	Rosmarinic acid, ferulic acid, caffeic acid, p-coumaric acid, chlorogenic acid, apigenin, myricetin, kaempferol	Erkan et al. 2011
4	*Sideritis arguta*	DPPH free radical scavenging and ABTS free radical scavenging activities	Acid hydrolysis of methanol, ethyl acetate, acetone extracts	Rosmarinic acid, ferulic acid, caffeic acid, p-coumaric acid, chlorogenic acid, quercetin apigenin, myricetin, kaempferol	Erkan et al. 2011
5	*Sideritis raeseri spp. Raeseri*	Hypotensive, vasorelaxant and cardiodepressant activities	Ethanol		Kitic et al. ,2012
6	*Sideritis syriaca*	Antioxidant and antimicrobial activity	Decoction	Hypoelatine, isoscutellarein diglucosides, verbascoside, martinoside, lavandulifolioside ve klorojenik asit	Goulas et al. 2014

7	*Sideritis scardica*	Anti-Alzheimer's activity	Methanol	Verbascoside, martynoside, echinacoside, lavandulofolioside, allysonoside, leucosceptoside, forsythoside, samioside, scutellarein, isoscutellarein, hypolaetin, and apigenin	Chalatsa et al. 2018
8	*Sideritis erytrantha subsp. erytrantha*	Antimicrobial activity	Essential oil	α-pinene, sabinene, B-caryophyllene, 1-caryophyllene, alfa-bisabolol	Altundag et al 2011
9	*Sideritis lotsyi var. mascaensis*	Analgesic and anti-inflammatory and no antimicrobial activity of the fractions against tested microorganisms	Water and chloroform fractions of ethanol extract		Hernandez-perez et al. 2002
10	*Sideritis brevibracteata*	Anti-inflammatory, antinociceptive, antioxidant and aldose reductase inhibitory activities	Methanol crude extract, chloroform, n-butanol and water fractions	Hypolaetin, Isoscutellarein, 30-Hydroxy-40-O-methylisoscutellarein, Verbascoside	Güvenç et al. 2010
11	*Sideritis condensata*	Insecticidal/acaricidal activity	Acetone	Linearol, isolinearol, siderol, sideridiol, sideroxol, 7-acetylsideroxol,and candol B	Kilic et al. 2009
12	*Sideritis albiflora*	Urease, tyrosinase and cholinesterase inhibitory activity	n-hexane, acetone, and methanol	Gallic acid, caffeic acid, p-coumaric acid, ferulic acid, trans 2-hydrocxycinnamic acid, rosmarinic acid, transcinnamic acid	Deveci et al. 2019
13	*Sideritis leptoclada*	Urease, tyrosinase and cholinesterase inhibitory activity	n-hexane, acetone, and methanol	Fumaric acid, caffeic acid, 2,4-Dihydroxy benzoic acid, ferulic acid, trans-2-Hydroxycinnamic acid, rosmarinic acid, transcinnamic acid	Deveci et al. 2019
14	*Sideritis erythrantha* var. *erythrantha* and *Sideritis erythrantha* var. *cedretorum*	Antioxidant and antimicrobial activities	Essential oil	α-pinene, β-Caryophyllene, β-pinene, sabinene, limonene	Köse et al. 2010

15	*Sideritis stritca*	Antioxidant, anticholinesterase, and anti-tyrosinase activities	Methanol and water	Fumaric acid, gallic acid, protocatechuic acid, p-hydroxybenzoic acid, catechin hydrate, 6,7-dihydroxy coumarin, 2,4-dihydroxybenzoic acid, caffeic acid, vanillin, p-coumaric acid, ferulic acid, coumarins, trans-2-hydroxycinnamic acid, ellagic acid, rosmarinic acid, and trans-cinnamic acid	Deveci et al. 2018
16	*Sideritis italica*	Antioxidant and antibacterial activities	Essential oil	Kaur-15-ene, b-Cubebene, Palmitic acid, p-Metoxyacetophenone	Basile et al. 2006
17	*Sideritis libanotica* ssp. *linearis*	Antioxidant activity	Methanol	(3' -O-methylhypolaetin 7-O-[6'''- O-acetyl-B-D-allopyranosyl-(1->2)]-6''-O-acetyl-B-D-glucopyranoside, sideridiol	Demirtas et al. 2009
18	*Sideritis germanicopolitana*	In vitro inhibitory effects on lipoxygenase (LOX), acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes associated with inflammatory and Alzheimer’s diseases	Methanol	5-allosyloxy-aucubine, melittoside, ajugol, five phenylethanoid glycosides, verbascoside, martynoside, leucoseptoside A, amalboside, decaffeoyl-verbascoside, four flavonoids, xanthomicrol, isoscutellarein 7-O-[6’’’-O-acetyl-b-allopyranosyl-(1->2)]-b- glucopyranoside, 4’-O-methylisoscutellarein 7-O-[6’’’-O-acetyl-b-allopyranosyl-(1->2)]- b-glucopyranoside, 3’-hydroxy-4’-O-methylisoscutellarein 7-O- [6’’’-O-acetyl-b-allopyranosyl-(1->2)]-b- glucopyranoside, dehydrodiconiferylalcohol 4-O-b-D-glucopyranose, pinoresinol 4’-O-b-glucopyranoside	Kırmızıpekmez et al. 2021
19	*Sideritis ozturkii*	Anti-inflammatory and antinociceptive activities	Acetone	Ozturkoside A, Ozturkoside B, Ozturkoside C	Küpeli et al. 2007
20	*Sideritis perfoliata*	Antiwrinkle, Hyper/Hypo-Pigmentation, Anti-Acne, Antimycobacterial Activity	Ethanol, essential oil	β-Phellandrene, α-pinene, β-pinene, Sabinene	Lall et al. 2019
21	*Sideritis raeseri*	Antioxidant/antiradical, antimicrobial activity	Essential oil	Geranyl-p-cymene, geranyl-γ-terpinene and geranyl-linalool	Mitropoulou et al. 2020

22	*Sideritis scardica*	Neuroprotective Activity against Alzheimer' disease	Petroleum ether, dichloromethane, methanol extracts and their fractions (diethyl ether, ethyl acetate, butanol)	Apigenin, myricetin-3-galactoside, and ellagic acid, Quercetin-3-O-rhamnoside, Myricetin-3-galactoside, vanillic acid, 4-hydroxybenzoic acid, caffeic acid, Luteolin-7-O-glucoside	Ververis et al. 2023
23	*Sideritis scardica*	Anti-skin Aging Activity	Ethanol	Isoscutellarein,4′-O-methylhypolaetin,4′-O-methylisoscutellarein	Sato et al. 2022
24	*Sidertis perfoliara*	Scocidal activity	Methanol	Fumaric acid, syringiic acid, caffeic acid, luteolin	Çelik et al. 2021
25	*Sideritis spylea*	Antioxidant activity	Water, acetone, ethanol, methanol		Nakiboglu et al. 2007
26	*Sideritis libanotica* subsp. *linearis*	Antimicrobial, antioxidant and anticholinesterase activities	Petroleum ether, acetone, methanol, water	Quinic acid, malic acid, chlorogenic acid, rosmarinic acid, coumarin, naringenin, luteolin, apigenin, kaempferol, rhamnetin	Ertas and Yener, 2020
27	*Stachys thirkei*	Antimicrobial, antioxidant and anticholinesterase activities	Petroleum ether, acetone, methanol, water	Quinic acid, malic acid, tannic acid, chlorogenic acid, rosmarinic acid, coumarin, naringenin, luteolin, apigenin	Ertas and Yener, 2020
28	*Sideritis ozturkii*, *Sideritis caesarea*	Antimicrobial and antioxidant activity	Methanol		Sagdic et al. 2008
29	*Sideritis raeseri* spp. *Raeseri*	Spasmolytic Activity	Ethanol		Brankovic et al. 2011
30	*Sideritis ozturkii*	Antioxidant, enzyme inhibitory (AChE inhibition, BChE inhibition, Tyrosinase inhibition, Amylase inhibition	Methanol, ethyl acetate, water	Chlorogenic acid, quercetin-3-O-glucoside, quinic acid, loganic acid, apigenin, gallic acid, ferulic acid, naringenin-7-O-glucoside, apigenin-7-O-glucoside	Zengin et al. 2019

Table 2. Anticancer activities, extracts and compounds of *Sideritis* species

No	*Sideritis* sp.	Compounds	Ekstract	Cancer cells	Methods	Activity	referances
1	*Sideritis leptoclada*	Quinic acid, malic acid, chlorogenic acid	Ethanol, ethyl acetate	Malignant melanoma cancer (HT-144)	MTT	Cells were significantly inhibited	Aydoğmuş-Öztürk et al. 2018
2	*Sideritis euboea*	2-(p-hydroxyphenyl)ethylstearate, β-sitosterol, stigmasterol, campesterol, ursolic acid, ursolic acid, eubol, eubotriol, 7-epicandicandiol, xanthomicrol, penduletin	Dichloromethane	DLD1, HeLa, A549)	MTT	Siderol exhibited potent cytotoxic activities	Tomou et al. 2020
3	*Sideritis trojana*	10-O-(E)-feruloylmelittoside, melittoside, 10-O-(E)-p-coumaroylmelittoside, stachysosides E. verbascoside, isoacteoside, lamalboside, leonoside A, isolavandulifolioside, isoscutellarein 7-O-[6‴-O-acetyl-β-allopyranosyl-(1→2)]-β-gluco pyranoside, 4′-O-methyisoscutellarein 7-O-[6‴-O-acetyl-β-allopyranosyl-(1→2)]-β-glucopyr anoside, 3′-hydroxy-4′-O-methyisoscutellarein 7-O-[6‴-O-acetyl-β-allopyranosyl-(1→2)]-β glucopyranoside	Methanol	PC3 prostate cancer	MTT	Only verbascoside showed cytotoxic activity	Kirmizibekmez et al. 2012

4	*Sideritis syriaca*	Gallic acid (GA), Protocatechuic acid (PCA), p-hydroxybenzoic acid (p-HA), cafeic acid (CA), chlorogenic acid (CHA), p-coumaric acid (p-Cou), ferulic acid (FA), o-coumaric acid (o-Cou), rosmarinic acid (RA) and trans-cinnamic acid	Methanol	Breast cancer cell line (MCF-7)	MTT	It exhibited strong cytotoxic activity at 100 and 250 µg/mL	Yumrutas et al. 2015
5	*Sideritis perfoliata*	Quercetin, resveratrol, alizarin, vanillic acid, caffeic acid, hydroxycinnamic acid, hydroxybenzoic acid, salicylic acid, acetohyroxamic acid	Methanol	Human cervical cancer cell lines (HeLa)	MTT	It exhibited dose-dependent activity of 25-200 µg/mL	Cocelli et al. 2021
6	*Sideritis montana*	Sideritins A and B. pomiferin E, 9α,13α-epi-dioxyabiet-8(14)-en-18-ol, paulownin, 6-methoxysakuranetin, 3-oxo-α-ionol and 4-allyl-2,6-dimethoxyphenol glucoside	Methanol	Human cervical cancer cell lines (HeLa, SiHa, and C33A)	MTT	While pomiferin e exhibited cytotoxic activity in HeLa cells, 6-methoxysakuranetin showed strong activity in C33A cells.	Tóth et al. 2017
7	*Sideritis libanotica* subsp. *linearis*		Methanol	Vero, HeLa and C6	BrdU	Extract showed cytotoxic activity on all cells tested	Demirtas et al 2009
8	*Sideritis perfoliata*		Ethanol	Human liver carcinoma (HepG2) and human cervical cancer (HeLa), non-cancerous Vero and HaCat cell	XTT	It showed moderate cytotoxic activity against HepG2 cells and antiproliferation activity against HeLa cells at high doses. Moderately toxic to Vero and HaCat cells at very high doses	Lall et al. 2019
9	*Sideritis pullulans*	Sideritone A, Sideritone B, Sideripullol A, Sideripullol B, Sideripullol C, Sideripullol D, *Sideritis*ide A, *Sideritis*ide B,	n-hexane, methanol	HeLa, PC3	MTT	All compounds tested showed cytotoxic activity at doses higher than 100 µM.	Faiella et al. 2014
10	*Sideritis raeseri*	Geranyl-p-cymene, geranyl-γ-terpinene and geranyl-linalool	Essential oil	Human immortalized keratinocyte (HaCat), human melananoma A375, human colon adenosarcoma Caco2, and human prostate carcinoma cell lines PC3 and DU145	MTT	It exhibited activity against all cells at doses of 0.114-0.216 mg/ml (EC50)	Mitropoulou et al. 2020

11	*Sideritis libanotica* subsp. *linearis*	Quinic acid, malic acid, chlorogenic acid, rosmarinic acid, coumarin, naringenin, luteolin, apigenin, kaempferol, rhamnetin	Petroleum ether, acetone, methanol, water	Human lung cancer cell line (A549)	MTT	Moderately toxic	Ertas and Yener 2020
12	*Stachys thirkei*	Quinic acid, malic acid, tannic acid, chlorogenic acid, rosmarinic acid, coumarin, naringenin, luteolin, apigenin	Petroleum ether, acetone, methanol, water	Human lung cancer cell line (A549)	MTT	Moderately toxic	Ertas and Yener 2020
13	*Sideritis cypria*	Melittoside, Geniposidic acid, Ajugoside, 8-epi-Loganic acid, Linearol, sidol, Apigenin, Acteoside, Leucosceptoside A, Lavandulifolioside, Lamalboside, Leonoside A, Chlorogenic acid,	Methanol and its fractions	Breast cancer cell line (MDA-MB231)	MTT	Methanol extract did not show cytotoxic activity. The isolated apigenin derivatives showed strong cytotoxic activity.	Lytra et al. 2021
14	*Sideritis niveotomentosa*	Propyl gallate, 1-Monolinoleoylglycerol trimethylsilyl ether,	Methanol, acetone	DLD1, HL60 and ARH77 cell lines	MTT	It showed strong cytotoxic effect at low IC50 against ARH77 cells, leaf extracts were cytotoxic in HL60 cells.	Sezer and Uysal 2021
15	*Sideritis perfoliata*	α-Humulene, trans-Caryophyllene, β-Phellandrene, Sabinene, α-pinene, β-pinene	Essential oil	Amelanotic melanoma (C32), renal cell adenocarcinoma (ACHN), hormone-dependent prostate carcinoma (LNCaP), and breast cancer (MCF-7) cell lines	SRB (protein-staining sulforodamine B)	It showed strong cytotoxic activity at doses of 100, 200, 400 μg/mL	Loizzo et al. 2007
16	*Sideritis scardica*		Hydro ethanol	Colon cancer (mouse colon adenocarcinoma cell line Colon 26)	WST-1	It showed strong cytotoxic activity at doses of 400 and 600 μg/mL	Dobrikova et al. 2023
17	*Sideritis ozturkii*	Chlorogenic acid, quercetin-3-O-glucoside, Quinic acid, loganic acid, Apigenin, gallic acid, ferulic acid, Naringenin-7-O-glucoside, Apigenin-7-O-glucoside	Water, ethyl acetate and methanol	Breast cancer cell line (MDA-MB231)	MTT	Methanol and ethyl acetate extracts showed strong cytotoxic activity	Zengin et al. 2019

When intrinsic apoptosis is stimulated, apoptotic proteins overwhelm antiapoptotic proteins, causing pores to open in the mitocondrial membrane and the release of factors such as cytochrome C, apoptosis initiating factor, smac/diablo (apoptosis inhibitor), OMI/HtrA2 (apoptosis inhibitor), endonuclease G from mitocondria to the cytosol. Then, DNA fragmentation occurs with the activation of stocromC-APAF1-caspase9 and finally with the activation of caspase3 (Savitskaya and Onishchenko, 2015 In the extrinsic apoptotic pathway, receptors and ligands on the cell membrane are involved. As a result of the binding of death ligands such as Tnf-alpha, FasL, TRAIL to Fas and TNF receptors, the death domain (DISC) located in the membrane becomes active and caspase 8 is activated. Caspase 8 either activates Bid and thereby initiates mitochondrial apoptosis or directly activates caspase 3. Caspase 3 activates the caspase 3 CAD enzyme, which is activated in both apoptotic pathways, and breaks DNA into short fragments (Savitskaya and Onishchenko 2015; Larsen and Sorensen 2017).

One of the most sought-after features in the fight against cancer is that the agents tested for anticancer activity selectively trigger apoptosis in cancer cells and have no side effects or weak effects on normal cells. Therefore, compounds obtained from plants are very valuable due to both their suppressive effects on cancer cells and their low side effects on normal cells. There are many studies showing that chemicals obtained from different plants induce apoptosis (Yumrutas et al. 2018; Cocelli et al. 2021). However, the number of studies showing the apoptotic effect of *Sideritis* species is limited. Aydoğmuş-Öztürk et al. (2018) showed that *S. leptoclada* ethanol extract caused an increase in the level of a cytokine such as TNF-alpha, which plays a role in immunity, inflammation, cell differentiation, control of cell proliferation and apoptosis. It has also been reported that ROS content increases in HT-144 melanoma cells due to the increase in TNF-alpha level and thus induction of apoptosis. Sezer and Uysal (2018) showed that as a result of exposing DLD-1 human colon cancer cells to *S. ozturkii* methanol and water extracts, the expression of the pro-apoptotic protein BAX and APAF gene increased significantly and the level of the anti-apoptotic gene BCL-2 decreased. In another study, after of the application of *S.* ozturkii ethyl acetate and methanol extracts (IC_{50} at doses of 65.36 µg/mL and 32.15 µg/mL) on breast cancer cell line, it was determined that the proliferation of the cells decreased depending on dose and time. However, only ethyl acetate extract has been shown to increase Bax expression and decrease Bcl-2 expression (Zengin et al. 2019). Moreover, Cocelli et al (2021) showed that *S. perfoliata* methanol extracts induced apoptosis in HeLa cancer cells at a dose of 200 µg/mL. It has been shown that BAX, APAF and Caspase3 mRNA levels increase after application of flower and leaf acetone and methanol extracts of *S. niveotomentosa* to DLD1, HL60 and ARH77 cells (Sezer and Uysal, 2021). Considering the literature examples mentioned above, it can be said that different extract groups of *Sideritis* species can induce apoptosis in different cancer cells. Although some extracts inhibit the survival and proliferation of cancer cells, they cannot induce apoptosis and therefore it should not be ignored that other death pathways may be activated. However, markers of both apoptotic and other death pathways need to be examined molecularly. Almost all of the studies mentioned here are cell-based in vitro studies, and most of the results of these studies have not been supported in vivo. Therefore, considering the phytochemicals of *Sideritis* species, more comprehensive apoptotic studies including animal experiments are needed.

6. Conclusion

In this review, the biological activities of *Sideritis* species and the phytochemicals such as phenolics, terpenoids and alkaloids that may be responsible for these activities are discussed. Many of *Sideritis* species have been shown to significantly reduce the viability of cancer cells and inhibit their proliferation. In addition to these effects, polar, semipolar and non-polar extracts of these species have been proven to induce apoptosis. Moreover, as a recommendation, it is thought that the anticancer activities of *Sideritis* species can be better understood by testing the effects of these species on death pathways such as ferroptosis, autophagy, necroptosis, as well as their metastasis and invasion suppressor properties in vitro and in vivo.

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