A Systematic Review of the Biological Activities of *Satureja* L. Species

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Summary

Since ancient, the genus *Satureja* L. is well recognized for its therapeutic values. Only recently, scientists have been aware of its new medicinal aspects. Therefore, we were interested to collect possible scientific data about this genus as a guide for researchers and to open a new road for pharmaceutical/medicinal exploration about it.
This information was gathered by using of scientific books, journals, articles and websites including Pubmed, Scopus, Scirus and Google Scholar without time limitation.
Different species of *Satureja* are famous for their analgesic, antiseptic, antimicrobial, antiviral, antioxidant, antiproliferative, antiprotozoal, antifungal, antidiarrheal, anti-inflammatory, anti-nociceptive and vasodilatory activities. The valuable therapeutic aspects of this genus are mostly correlated to the existence of essential oils, flavonoids and triterpenoids.
In summary, the combination of two or more subspecies acting on different mechanisms to produce a synergistic effect should be considered. Based on our knowledge only few attempts have done towards the recognition of the clinical aspects of this genus while current data mostly highlights *in vitro* examinations. However data are inconclusive yet and desire further scientific attempts to confirm the traditional information or to investigate novel medicinal aspects of this genus. Future works are necessary to prove the efficacy and edibility of these essential oils in both animal and human.

Keywords: *Satureja* spp; biological effect; animal; human; composition.

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Introduction

Humans live in a world surrounded with miraculous green elements that have been crammed with numerous discovered/undiscovered therapeutic components, plants. Plants are naturally gifted at the synthesis of medicinal compounds and have been used successfully for centuries by herbalists, healers and people all over the world and especially in Africa, Asia and Latin America. The selection of medicinal plants is a conscious process, which has led to an enormous number of medicinal plants being used by the numerous cultures of the world[1]. According to the World Health Organization (WHO), about 65-80% of the world's population in developing countries, due to poverty and lack of access to modern medicine, depends essentially on plants for their primary health care[2]. Nowadays, at least 25% of the active compounds in currently prescribed synthetic drugs were first identified in plant resources[3] and 20000 plants have been used for medicinal proposes which, 4000 have been used commonly and 10% of those are commercial.

Description and distribution of Satureja spp.

The genus *Satureja* L. (savory) belongs to the family Lamiaceae (labiatae), subfamily Nepetoidae and tribe Mentheae. This genus contains about 200 species of aromatic herbs and shrubs, largely distributed in area stretching from the Mediterranean region to Europe, West Asia, North Africa, the Canary Islands, and South America. The *Satureja* spp. are annual or perennial aromatic herbaceous with dark green or grey-greenish leaves which grow in the arid, sunny, stony and rocky environments. Wholly dried parts and typically, above ground parts contain medicinal values and are used as remedies. The species rise up in temperate regions up to 45-60 cm high. They grow up in well-drained neutral alkaline dry soil. Over 30 species of this genus are distributed in eastern parts of Mediterranean area[4].

The known characteristic of the subfamily Nepetoideae is that its representatives contain more than 0.5% of essential oil[5]. Additionally, the high quantity of thymol in the essential oils might express the presence of thyme or origano like odor in different species. Some of the *Satureja* spp. are known as 'thyme' or 'Kekik'. Kekik is a common name given to various Labiatae (lamiaceae) species, including species of *Thymus, Origanum, Corydothymus* and *Thymbra* genera[6].

Applications of Satureja spp.

Due to the simplicity of cultivation, eminent ethno-medical activity, having both food and pharmaceutical importance, this genus is being used worldwide as herbal beverages, spices, food additives and flavoring. Moreover, the essential oils of the species have been used in the perfume and cosmetic industries, either alone or with other essential oils[7]. Traditionally, in folk medicine the savory species are extensively utilized as; muscle pain reliever, tonic and carminative in treating stomach and intestinal disorders such as cramps, nausea, indigestion and diarrhea[8]. Recently, the other properties of *Satureja* spp. such as; antibacterial, antifungal, antioxidant, anti-diabetes, anti-HIV, anti-hyperlipidemic, reproduction stimulatory, expectorant and vasodilatory activities have been demonstrated[9-15]. It has also been reported that in east Africa, roots and leaves of some species (*S. biflora* and *S. pseudosimensis* Brenan.) are used for the treatment of headache, coughs and to scent public places[16]. In addition, there are remarkable evidences in Iranian and Turkish ancient medical books, that *S. hortensis* has remedial effect on respiratory diseases and has been used orally to cure asthma and coughs.

Major components of Saturja spp.

The essential oils obtained from different species of this genus have certain biological functions such as physiological function (in plant metabolism) and ecological function (in interactions of the plants with their environment). Moreover, it has been reported there are remarkable differences between and within the chemical composition of the essential oils of *Satureja* subspecies[17]. Phytochemical studies have revealed volatile oils, tannins, phenolic compounds, sterols, acids, gum, mucilage and pyrocatechol are the main components of *Satureja* species. The major constituents of the essential oils in most species are found to be phenols, carvacrol, thymol, *p*-cymene, *β*-caryophyllene, linalool, monoterpenes, sesquiterpenes, alcohols, phenolic acids, labiatic acids and flavonoids[18].

Methods

The data presented in this review were collected by using of scientific and encyclopedia books, journals, articles and websites Pubmed, Scopus, Scirus and Google Scholar without time limitation.

Results and Discussion

Satureja spp. and antioxidant properties

Plenty of studies verify the antioxidant activity of *Satureja* subspecies[19-21]. Antioxidants are compounds, which inhibit or delay the oxidation of other molecules by inhibiting the initiation or propagation of oxidizing chain reactions. Recently, the consumption of natural antioxidant that occur in all higher plants and in all parts of them, has risen up regarding the side effects of synthetic ones[22].

As mentioned before, the oils of genus *Satureja* are being filled with isopropanoids such as carvacrol, thymol, flavonoids, *β*-caryophyllene, *γ*-terpinene, *p*-cymene and linalool, which are expected to possess strong antioxidant effects[23]. It has been described that the antioxidant effect of aromatic plants might be due to the existence of hydroxyl groups in their phenolic compounds. The constituents containing hydroxyl group exhibited relatively strong antioxidant effect in *S. montana*[21]. The essential oil of *S. cilicica* exhibited significant antioxidant activity in butter during the storage. Antioxidant activities of the oils were higher when their concentrations were increased. As a result of the study, the essential oil of *S. cilicica* was suggested to be used as natural antioxidant and aroma agent in butter[24].

Satureja spp. and anti-infection properties

The most important sources of infections that engage both flora and fauna are known as bacteria, fungi and viruses. Plants produce essential oils as secondary metabolites, either genetically or in response to pathogens/stress to protect them against natural enemies. In general, the essential oils are natural products preventing the growth of pathogens. There are sufficient articles highlighting the antibacterial and antifungal activities of genus *Satureja* but only few ones are found to verify its antiviral activity. The antimicrobial activity of *Satureja* spp. was first reported during 1950s and it was established that the inhibitory effect of savory is likely due to its high content of thymol and carvacrol, which are among the most efficient herbal antibacterial agents known[25]. Generally, antibacterial activity of essential oils depend on the type, composition and concentration of the oils, the type and concentration of the target microorganism, the composition of the substrate and the processing/storage conditions[26]. The concentration of essential oils in *S. thymbra* and *S. parnassica* is known to be fluctuated. Those oils which were obtained during the flowering period

were found the most potent in exhibiting the lowest minimum inhibitory concentration (MIC) values and retaining considerable antibactericidal properties[27].

The essential oils have been proven to be inhibitory against a wide range of food spoiling microbes, dependent upon their concentration, method of testing and active constituents present[28]. Furthermore, different species of *Satureja* has been investigated extensively against foodborn pathogens. The monoterpene hydrocarbons and phenolic monoterpenes are the main constitutes of the isolated essential oils from endemic *Satureja* spp. in Greece with remarkable antibacterial activities against foodborne pathogens[29].

The antifungal activities of the essential oil, hydrosol, ground material and extract of summer savory (*S. hortensis* L.) on mycelial growth of two fungi (food fungi) has been studied[30]. All doses of extract exhibited a dose-dependent fungicidal effect. In *S. thymbra*, carvacrol was found to be the main antifungal component followed by monoterpene hydrocarbons *c*-terpinene and *p*-cymene[31].

The efficiency of *S. boliviana* against two different viruses-HSV-1 and VSV has been studied[32]. The aqueous extract of *S. montana* showed potent anti-HIV-1 activity and the active components in the extract were found to be water-soluble polar substances, not nonpolar compounds such as essential oils[15].

Satureja spp. and anti-diabetes properties

Diabetes is a chronic metabolic disorder that continues to present a major worldwide health problem. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hyperglycemia and disturbances of carbohydrates, lipid and protein metabolism[33].

Despite the awareness of the therapeutic values of genus *Satureja* only few studies have noticed to its anti-diabetes effects. A significant decrease in fasting blood

glucose was observed with essential oil of *S. khuzestanica* in diabetic rats[9]. Administration of the essential oils from *S. khuzestanica* prevented malathion (a commonly used organophosphorus)-induced changes on blood glucose, acetylcholinesterase activity, mitochondrial glycogenolysis and gluconeogenesis in liver of a subchronic exposure rat model[11]. The authors concluded that this activity is mediated through the antioxidant potential of *S. khuzestanica* essential oil and increasing of acetylcholinesterase activity. In another investigation it was shown that administration of *S. khuzestanica* essential oil did not affect the concentration of blood glucose but could decrease hepatic phosphoenolpyruvate carboxykinase activity and increased hepatic enzymes glycogen phosphorylase in rat. This study has also discussed that the interruption of hepatic glucose metabolism is anticipated as a mechanism of anti-diabetic action of *S. khuzestanica* essential oil, which could be in relation with antioxidant property of this plant[34]. In a new publication, the usage of *S. khuzestanica* as a supplement to drug regimen of diabetic type 2 patients with hyperlipidemia has been recommended[35].

Satureja spp. and anti-hyperlipidimic properties

The accumulation of hypertension with hyperlipidemia enhances the risk of cardiovascular disease. It has been well established that hypercholesterolemia is related with various pathological disorders such as cardiovascular diseases, diabetes mellitus, atherosclerosis, and thromboembolic disorders. The administration of flavonoids isolated from *S. hortensis* along with cholesterol in rabbits has resulted in a significant reduction of serum cholesterol[36]. Rats in treatment with essential oils of *S. khuzestanica* exhibited significant reduction in normal blood lipid peroxidation level and enhancement of total antioxidant power. The antioxidant properties of *S. khuzestanica* essential oil may explain its triglyceride-lowering effects[9]. In addition,

the main constituents of *S. khuzstanica* are isopropanoids such as carvacrol, thymol and flavonoids. It has been shown that thymol and carvacrol significantly decrease the serum cholesterol levels. Flavonoids have also shown anti-hyperlipidemic properties[37].

Satureja spp. and reproduction stimulatory effects

Study on the effect of *S. khuzestanica* essential oil on male rat fertility has revealed significant improvements in potency, fecundity, fertility index, and litter size. Additionally a significant decrease in post implantation loss has been observed[38]. Furthermore, concentration of FSH, testosterone and the weights of tests, seminal vesicles and ventral prostate were significantly increased. These changes might be in association with antioxidant potential of the essential oils. As explained before, *p*-cymene, carvacrol and flavonoids are the major antioxidants in *Satureja* spp. thus it might explain the reproduction stimulatory effects of this genus.

Satureja spp. species and analgesic activity

Lamiaceae is known as a family with great antispasmodic and bone pain reliever activities. Peppermint, rosemary, balm, savory and sage oil are well recognized for their relaxant effect on smooth muscles. As mentioned, phytochemical exploring on *Satureja* spp. exposed that carvacrol, other monoterpene hydrocarbons in its essential oil, flavonoids and phenolic acids were the main group of compounds of the aerial parts. In the manner of screening of *Satureja* spp. for smooth muscle relaxant properties, some publications suggested flavonoids are the main components with anti-nociceptive properties while the others concluded that carvacrol plays the main role. It has been revealed the essential oil of *S. hortensis* has a relaxant effect on isolated ileum *in vitro* similar to that of dicyclomine[13]. In their discussion carvacrol

recognized as the main constituent of *S. hortensis* essential oil with analgesic property consistent its contribution in spasmolytic activity. Naringenin, eriodictyol and luteolin, isolated flavonoids from *S. obovata* exhibited significant relaxant effects on vascular smooth muscles[18] while eriodictyol (5,7,3′,4′ -tetrahydroxyflavanone), isolated from same species showed slight vasodilatory activity in rat thoracic aorta[39]. Generally, the anti-inflammatory and antinociceptive effects are investigated by using of carrageenan-induced paw edema and formalin test respectively[40]. The essential oil of *S. hortensis* has illustrated significant antinociceptive effect in formalin test in rats. In this test, the first or acute phase is thought to result from direct chemical activation of nociceptive afferent fibers and the second or tonic phase is an inflammatory process[41]. *S. khuzistanica* exhibited a similar anti-inflammatory activity as indomethacin in carrageenan test[10]. The plant showed antinociceptive activity in a dose-dependent manner at the second phase of formalin test. This study confirmed that anti-inflammatory and anti-nociceptive properties of *S. khuzistanica* are comparable to those of indomethacin and morphine. In their conclusion presence of flavonoids, steroids, essential oil, mainly carvacrol and tannin were introduced responsible for anti-inflammatory and antinociceptive activities of this genus. In a further study by Ghazanfari et al. (2006) it was clarified that the beneficial effect of *S. khuzestanica* essential oil on the mouse model of inflammatory bowel diseases was comparable to that of prednisolone (positive control) [42]. Few investigations pointed that some species does not show any anti-inflammatory effects. It has been established that *S. thymbra* L. essential oil does not exert any anti-inflammatory effect while it may have central analgesic activity in mice and rats[43].

Satureja spp. and toxicity

Generally, essential oils contain great number of constituents, thus it seems they have no specific cellular targets. The cytotoxic activity of essential oils is mostly due to the presence of phenols, aldehydes and alcohols[22]. According to the literatures, there are conflictions about the safety and toxicity of various species of *Satureja*. It seems necessary to differ between the cytotoxic effects of *Satureja* spp. on microorganisms (bacteria, fungi, yeast and viruses) and its toxic effects in eukaryotic cells. In spite of adequate publications concerning the anti-pathogenic activity of *Satureja* spp. many people are consuming the subspecies as herbal tea, spices and additives every day worldwide. For instance, *S. hortensis* is consumed as a vegetable by people every day and has no known adverse effect[13]. In addition, both ethanolic extract and the essential oil of *S. hortensis* exhibited protective effects on rat hydrogen peroxide-induced damage on lymphocytes *in vitro*[44]. The essential oil of *S. Khuzestanica* has shown a protective effect against the toxicity of malathion (a commonly used organophosphorus) in rats[11]. Another study showed marked toxicity of two isomeric monoterpene peroxides isolated from the leaves of *S. gilliesi* toward Artemia salina (brine shrimp bioassay) [45].

Chemical composition of Satureja spp.

Literature reviews verify recognizable variation in chemical composition of the oils of different *Satureja* species within or between them. The oils composition depends on climatic, seasonal and geographic conditions, harvest period and distillation technique[26]. Figure 1 portraits the chemical structure of the main compounds isolated from *Satureja* spp. The biological activities and the major components isolated from the most common species of *Satureja*. have been depicted in Table 1.

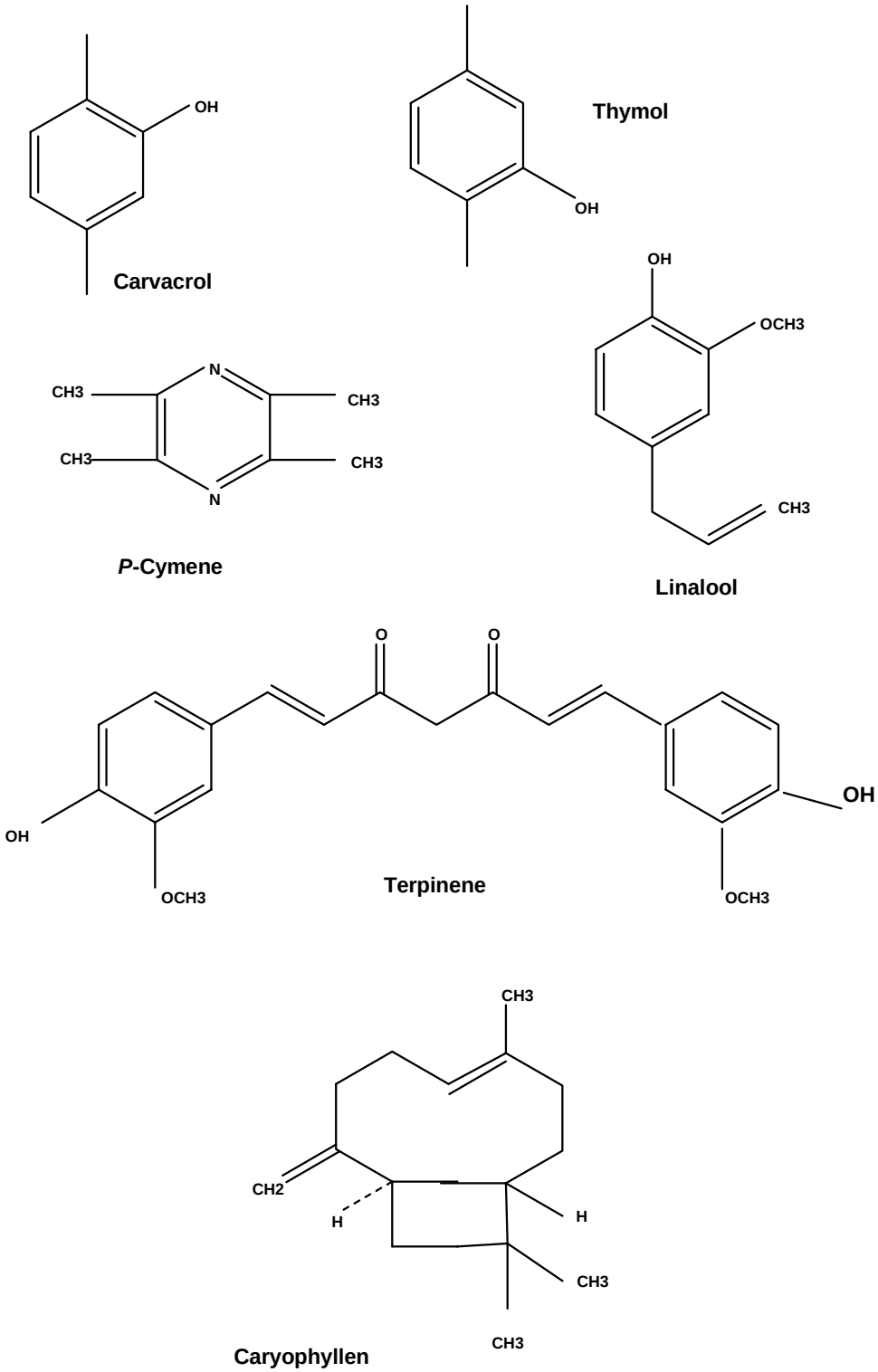

Figure 1. Chemical structures of the main compounds isolated from genus *Satureja* L.

Table 1. Different species of *Satureja* L. with their biological activities and the major compounds

Plant species	Part used	Common usage	The most effective component(s)	Country of origin	Study references (author name and number)
S. hortensis L. (summer savory)	Aerial parts	muscle pain reliever, tonic and carminative in treating stomach and intestinal disorders, food and beverages flavoring, antioxidant, antibacterial, antifungal, inhibitory effect on oxidative DNA damage, antihyperglycemic	carvacrol, *γ*-terpinene, thymol and *p*-cymene	Turkey, Iran	Hajhashemi et al., 2000; (Zargari, 1990); Madsen et al., 1998; Gulluce et al., 2003; Sahin at al., 2003; Behravan et al., 2006; Mchedlishvili et al., 2005 (13, 8, 20, 49,14, 44, 36)
S. montana L. (winter savory)	Aerial parts	bactericidal, carminative, digestive, expectorant, fungicidal, laxative, antidiuretic, sedative, antioxidant activity, flavoring	thymol, *p*-cymene, carvacrol, *γ*-terpinene, flavonoids, triterpenes	Turkey, Iran	Oussalah et al., 2006; Mastelic and Jerkovic, 2002 (25,50)
S. spicigera (C. Koch) Boiss.	Aerial parts	antibacterial	thymol, *p*-cymene, *γ* -terpinene and carvacrol	Turkey, Iran	Sefidkon and Jamzad, 2004; Azaz et al., 2005 (47, 51)
S. obovata Lag. (Iberian savory)	Aerial parts	smooth muscle relaxant	flavonoids	Turkey	Duke and Beckstorm-Sternberg, 2001; Sanchez de Rojas et al., 1996 (52,18)
S. thymbra L. (goat oregano)	Aerial parts	Antifungal, antinociceptive, anti-inflammatory	carvacrol and *γ*-terpinene	Turkey	Glamoclija et al., 2006; Sokovic et al., 2002; Ulku Karabay-Yavasoglu et al., 2006 (53, 31, 43)
S. cuneifolia Ten. (wild savory) or (cuneate Turkish savory)	Aerial parts	Antibacterial, carminative and antidiabetes	carvacrol and *γ*-terpinene	Turkey	Aydin and Oztiirk, 1996; Baydar et al., 2003 (6, 26)
S. kitaibelii Wierzb. ex Heuff.	Aerial parts	-	*p*-cymene, geraniol and *β*-elemene	Turkey	Slavkovska et al., 2000 (17)
S. boissieri Hausskn. ex Boiss.	Aerial parts	condiment, herbal tea	carvacrol, *γ*-terpinene and *p*-cymene	Turkey	Kurkcuoglu et al., 2001 (54)
S. wiedemanniana (Lallem.) Velen	Aerial parts	antibacterial	carvacrol, thymol, *p*-cymene and *γ*-terpinene	Turkey	Baser et al., 2001 (55)
S. macrantha	Aerial parts	antibacterial, antifungal	carvacrol	Turkey	Azaz et al., 2005 (51)
S. aintabensis	Aerial parts	antibacterial, antifungal	p-cymene	Turkey	Azaz et al., 2005 (51)
S. coerulea Janka	Aerial parts	antibacterial	germacrene-D	Bulgaria, Turkey	Tumen et al., 1998 (64)
S. icarica P.H. Davis	Aerial parts	antibacterial	carvacrol	Greece, Turkey	Tumen et al., 2000 (56)
S. pilosa Velen	Aerial parts	antibacterial	-	Bulgaria, Greece, Turkey	Tumen et al., 2000 (56)
S. khuzestanica jaezad.	Aerial parts	antioxidant, antidiabetic, anti-hyperlipidemic, reproduction stimulatory properties, antibacterial, anti-inflammatory, antinociceptive	*p*-cymene and carvacrol	Iran	Abdollahi et al., 2003; Amanlo et al., 2005; Basiri et al., 2007; Haeri et al., 2006; Saadat et al., 2004 (9, 10, 11, 38, 34)
S. sahendica Bornm.	Aerial parts	culinary herbs	thymol, *p*-cymene and *γ*-terpinene	Iran	Sefidkon et al., 2004 (7)

S. mutica Fisch. & C. A. Mey.	Aerial parts	antimycotic acitivity	carvacrol, thymol, *γ*-terpinene, *p*-cymene and methyl thymol	Iran	Behravan et al., 2004; Gohari et al., 2005; Sefidkon and jamzad, 2004 (57, 58, 47)
S. macrantha C. A. Mey.	Aerial parts	Antibacterial, antifungal	*carvacrol, p*-cymene, limonene and thymol	Iran	Azaz et al., 2005; Sefidkon and Jamzad, 2004 (51, 47)
S. intermedia C. A. Mey	Aerial parts	-	thymol, *γ*-terpinene and *p*-cymene	Iran	Sefidkon and Jamzad, 2004 (47)
S. parvifolia (Phil.) Epl. (small-leaf Pampa savory)	-	antibacterial, antifungal, relaxant effect	piperitone oxide	Argentina	Duke and Beckstorm-Sternberg, 2001; Viturro et al., 2000; Zygadlo and Grosso, 1995 (52, 46, 59)
S. boliviana Briq.	-	antiviral, gastric cytoprotection, insecticidal activity	*γ*-terpinene, *β*-caryophyllene and germacrene D	Bolivia	Abad et al., 1999; Laurent et al., 1998; Viturro et al., 2000 (32, 60, 46)
S. gilliesii	-	toxicity toward Artemia salina (brine shrimp bioassay)	mono and sesquiterpene peroxides	Chilea, tropical America	Labbe et al., 1993 (45)
S. subspicata Vis.	Aerial parts	antibacterial, antifungal	carvacrol, *α*-pinene, *p*-cymene, *γ*-terpinene and thymol methyl ether	Croatia	Skocibusic et al., 2005 (28)
S. spinosa L.	-	bactericidal properties	monoterpene hydrocarbons, and phenolic monoterpenes	Greece, Switzerland	Chorianopoulos et al., 2004 (29)
S. parnassica Heldr. & Sart ex Boiss.	-	antibacterial	caryophyllene, carvacrol, caryophyllene oxide, spathulenol, *p*-cymene and linalool	Greece, Turkey,	Chorianopoulos et al., 2006; Tzakou and Skaltsa, 2003 (27, 61)
S. douglasii (Benth.) Briq. (Douglas savory)	Whole plant	-	monoterpenes	North America	Duke and Beckstorm-Sternberg, 2001 (52)
S. glabella (Michx.) BRIQ. (smooth savory)	Whole plant	-	germacrene D, isomethanol, menthone and limonene	North America	Duke and Beckstorm-Sternberg, 2001 (52)
S. grandiflora L. (French savory)	shoot	-	germacrene D, isomethanone, pulegone and methanol	North America, Southwest Bulkan, Turkey	Duke and Beckstorm-Sternberg, 2001 (52)
S. acinos L.	-	-	triterpenes, oleanolic, ursolic, crataegolic acid ,naringenin, rutinoside and eriodictyol	Sweden, Spain	Escudero et al., 1985 (62)
S. brownei (SW.) Briq.	-	antibacterial (against respiratory infections)	pulegone and menthone	Venezuela, Guatemala	Caceres et al., 1991; Rojas and Usubillaga, 2000 (63, 48)

Conclusion

Essential oils isolated from members of the genus *Satureja* have been used both commercially (as food and beverages flavoring and in perfume/cosmetic industries) and therapeutically for centuries while traditionally the most commonly used species are *S. montana, S. hortensis* and *S. thymbra*. There is a remarkable variety in chemical composition of the *Satureja* spp. oils. For instance, the major constituent of *S. parvifolia* oil is piperitone oxide[46] and those of *S. boissieri* are carvacrol and γ-terpinene[47]. According to some reports, the dominant components in the oil of *S. montana* are caryophyllene and geraniol while according to other reports it is carvacrol[17]. Menthone and isomenthone are the main components of the oils of *S. boliviana* and *S. brevicalix* from Peru. The major constituents in *S. khuzistanica* have been detected as *p*-cymene and carvacrol[47], whereas those of *S. brownei* were pulegone and menthone[48]. Thymol, carvacrol, γ-terpinene and *p*-cymene were found to be the main components in the essential oil of *S. hortensis*. Amongst the claims concluded for savory oils, the antibacterial, antifungal, antiviral, antioxidant, antidiarrheal, vasodilatory activities, carminative (smooth muscle relaxing), sedative, and anti-diabetes are most applicable. In this review, we tried to highlight the current state of knowledge about the therapeutic effects of *Satureja* oils on animal health. Although the data are still inconclusive and it desires further scientific attempts to confirm the traditional information or to investigate novel medicinal aspects of this genus. Studies on different species of *Satureja* illustrated variations in outcomes such as the amount of essential oils, composition of isolated compounds and usage of the same species in different cultures. Nevertheless, critical point is the lack of clinical and *in vivo* tests to prove the medicinal values of this genus. Despite of several animal studies, only one clinical trial has been performed for *Satureja*[35].

However, improvement of oils isolation and identification methods, biological examinations and clinical trials seem necessary to demonstrate the remedial significance of *Satureja* spp. Future works are necessary to explore the efficacy and edibility of these essential oils.

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