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An Update on Pharmacology of *Satureja* Species; From Antioxidant, Antimicrobial, Antidiabetes and Anti-hyperlipidemic to Reproductive Stimulation

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Abstract: Since ancient, the genus *Satureja* L. is well recognized for its therapeutic values. Only recently, scientists have been aware of its new medicinal aspects. In our last review, we evaluated existing scientific data about this genus. Regarding ongoing reports and new multi-functional properties of this plant we were interested to update pharmacology of *Satureja*. Data were gathered using of scientific books, journals, articles and websites including Pubmed, Scopus and Google Scholar up to 25th April 2010. Of initial search, 1540 records were reviewed for inclusion or exclusion in study, of which 71 publications were included. Different species of *Satureja* are famous for their analgesic, antiseptic, antimicrobial, antiviral, antioxidant, antiproliferative, antiprotozoal, antifungal, antidiarrheal, anti-inflammatory, anti-nociceptive, anticholinesterase and vasodilatory activities. The valuable therapeutic aspects of this genus are mostly correlated to the existence of essential oils, flavonoids and triterpenoids. The combination of two or more subspecies acting by different mechanisms to produce a synergistic effect should be considered. Based on the conducted assessments so far, antibacterial, antifungal, antiviral, antioxidant, anti-diabetic, vasodilatory and analgesic activities are characterized as the most applicable properties of *Satureja* subspecies. Further studies are needed to confirm novel pharmacological aspects of this genus in both animal and human.

Key words: *Satureja*, pharmacology, toxicology, animal, human

INTRODUCTION

Accessibility and affordability of the medicinal herbs have made them as fundamental part of many people's life all over the world. 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 (Heinrich *et al*., 2004). Surveys conducted in Australia and US indicates that almost 48.5 and 34% of individuals had used at least one form of unconventional therapy, including medicine, respectively (Kim *et al*., 2007). 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 (Calixto, 2005). Regarding the lack of safe modern drugs, evaluation of effective plants for diseases like diabetes has been recommended by WHO (Kim *et al*., 2007). In the recent years, efficacy of herbal medicines in diseases like inflammatory bowel disease (Rahimi *et al*., 2009; Rezaie *et al*., 2007), obesity (Hasani-Ranjbar *et al*., 2009a), diabetes (Rahimi *et al*., 2005), pancreatitis (Monfared *et al*., 2009), inflammatory and oxidant-related diseases (Hasani-Ranjbar *et al*., 2009b; Rahimi *et al*., 2010) has been systematically reviewed. It is estimated that close to 25% of the active compounds in currently prescribed synthetic drugs were first identified in plant resources (Halerstein, 2005) and 20000 plants have been used for medicinal proposes which, 4000 have been used commonly and 10% of those are commercial.

The genus *Satureja* L. (savory) belonging to the family Lamiaceae (labiatae), subfamily Nepetoidae and tribe Mentheae contains about 200 species of aromatic herbs and shrubs that are grown in Middle East, Mediterranean region to Europe, West Asia, North Africa, the Canary Islands and South America. Over 30 species of this genus are distributed in eastern parts of Mediterranean area (Cantino *et al*., 1992). The known characteristic of the subfamily Nepetoideae is that its representatives contain more than 0.5% of essential oil. Moreover, remarkable differences between and within the

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chemical composition of the essential oils of *Satureja* subspecies has been found (Slavkovska *et al*., 2001). Phytochemical studies have revealed volatile oils, tannins, phenolic compounds, sterols, acids, gum, mucilage and pyrocatechol as the main components of *Satureja* species. The major constituents of the essential oils from savory species are phenols, carvacrol, thymol and flavonoids (Sefidkon *et al*., 2004). Regarding existence of high amount of thymol and carvacrol in *Satureja* species, good smelling and simple cultivation, they are used as a flavoring compound in food, pharmaceutical and cosmetic industries. Savory species have been traditionally used as muscle pain reliever, tonic and carminative in treating stomach and intestinal disorders such as cramps, nausea, indigestion and diarrhea (Zargari, 1990). In the last five years, other properties of *Satureja* species such as antibacterial, antifungal, antioxidant, anti-diabetes, anti-HIV, anti-hyperlipidemic, reproduction stimulatory, expectorant and vasodilatory activities have been demonstrated (Abdollahi *et al*., 2003; Amanlou *et al*., 2005; Basiri *et al*., 2007; Deans and Svoboda, 1989; Hajhashemi *et al*., 2000; Sahin *et al*., 2003; Yamasaki *et al*., 1998; Vagionas *et al*., 2007; Vosough-Ghanbari *et al*., 2008).

An extensive review of the literature regarding biological and composition of *Satureja* species has been already published. The aim of this review is to complete on previous data specially those provided since the publication of the above-mentioned reviews. The present work is an update on pharmacology of *Satureja* up to May 2010.

MATERIALS AND METHODS

The data presented in this review were collected using all scientific data come from encyclopedia books, journals, articles and websites Pubmed, Scopus, Scirus and Google Scholar up to 25th April 2010. Of initial search, 1540 records were reviewed for inclusion or exclusion in study, of which 71 publications were included.

RESULTS AND DISCUSSION

As *Satureja* sp. are consumed commonly, their possible beneficial health effects have faced a great deal of attention. 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 (Bakkali *et al*., 2008). Antioxidant activity of *Satureja* subspecies have been confirmed in many studies (Exarchou *et al*., 2002; Madsen *et al*., 1998; Radonic and Milos, 2003). 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 (Ruberto and Baratta, 2000). The constituents containing hydroxyl group exhibited relatively strong antioxidant effect in *S. Montana* (Radonic and Milos, 2003). Newly, *S. khuzestanica* essential oils (SKEO) was found to protect rat reproductive system from toxicity of cyclophosphamide that is currently used an anticancer alkylating agent having adverse effect on male reproductive tract (Rezvanfar *et al*., 2008). In a related study, SKEO protected rats from cyclophosphamide-induced Hemorrhagic Cystitis (HC) by reduction of free radical-induced toxic stress (Rezvanfar *et al*., 2010). Interestingly, the essential oil of *S. cilicica* has been suggested for usage as a natural antioxidant and aroma agent in butter in a dose dependent manner (Ozkan *et al*., 2007).

Generally, production of essential oils by plants is a source of self protection against environmental pathogens. Antibacterial activity of essential oils depends on the type, composition and concentration of the oil, the type and concentration of the target microorganism, the composition of the substrate and the processing/storage conditions (Baydar *et al*., 2004). 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 (Chorianopoulos *et al*., 2006).

As yet, carvacrol and thymol play the fundamental roles in antimicroorganism activity of this genus. In an interesting study in Turkey, carvacrol the major constituent of the essential oil of *S. spicigera* was tested against 25 phytopathogenic bacterial strains and exhibited potent antibacterial activity over a broad spectrum of the bacteria. Their results demonstrated that *S. spicigera* oil could be used to control agricultural plant pathogenic bacteria and as a seed disinfectant (Kotan *et al*., 2010). Of fifty-five compounds isolated from the oil of *S. cuneifolia*, linalool and α-pinene were found to be the dominant compounds. The oil exhibited a complete inhibition of the growth of mostly all tested microorganisms at the lowest supplied concentration.

Antifungal activity of the different species of savory have been reported frequently (Boyraz and Ozcan, 2006; Sokovic *et al*., 2002). Potent antiviral activities of *S. boliviana* (against viruses-HSV-1 and VSV) and *S. montana* (against HIV-1) have been proven by Abad *et al*. (1999) and Yamasaki *et al*. (1998), respectively.

Up to date, limited investigations have noticed to the anti-diabetes effects of *Satureja* sp. Anti-diabetic activity of *S. khuzestanica* has been proven in several studies.

It is thought that this activity is mostly mediated through antioxidant potential of this genus (Basiri *et al*., 2007; Saadat *et al*., 2004). The antioxidant property of *S. khuzestanica* is also known as a reasonable explanation for its triglyceride-lowering effects (Abdollahi *et al*., 2003). The investigation showed that carvacrol, thymol and flavonoids (the main constituents of *S. khuzestanica* essential oil) are responsible to marked reduction of serum cholesterol levels in diabetic patients. Confirming those findings, Mchedlishvili *et al*. (2005) explained flavonoids isolated from *S. hortensis* responsible for reduction of cholesterol level in rabbits. Study on the effect of SKEO 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 (Haeri *et al*., 2006).

Lamiaceae is well recognized as a family with great antispasmodic and pain reliever properties. Due to the broad distribution of the species of the genus *Satureja*, various compounds are recognized responsible for its analgestic effect. For instance, three known flavonoids (naringenin, eriodictyol and luteolin) isolated from *S. obovata* exhibited significant relaxant effects and (De Rojas *et al*., 1999) while eriodictyol (5,7,3',4' -tetrahydroxyflavanone) isolated from same species showed slight vasodilatory activity in rats and (De Rojas *et al*., 1999). Two studies clarified SKEO has beneficial anti-inflammatory effects comparable to those of prednisolone, indomethacin and morphine (positive controls) (Amanlou *et al*., 2005; Ghazanfari *et al*., 2006). In contrast, some species does not show any anti-inflammatory effects. The essential oil of *S. thymbra* L. did not show any anti-inflammatory effect while it caused central analgesic activity in mice and rats (Karabay-Yavasoglu *et al*., 2006).

Despite the conflictions about the safety and toxicity of various species of *Satureja*, many people are consuming the subspecies as herbal tea, spices and additives every day worldwide. As earlier mentioned it is necessary to differ between the cytotoxic effects of the subspecies on microorganisms and its toxic effects in eukaryotic cells. The essential oils of *S. hortensis* and *S. khuzestanica* exhibited protective effects against the toxicity of hydrogen proxide and malathion in rats, respectively (Behravan *et al*., 2006; Basiri *et al*., 2007). Another study revealed that SKEO protects reproductive system from toxicity of cyclophosphamide. Co-administration of SKEO significantly improved cyclophosphamide-induced changes in plasma testosterone, sperm quality, spermatogenesis, fertility, toxic stress and DNA damage (Rezvanfar *et al*., 2008). The biological activities and the major components isolated from the most common species of *Satureja*. have been depicted in Table 1.

Table 1: *Satureja* L. subspecies with their therapeutic indications

Botanical and species	Local name	Therapeutic indications	Effective component	Reference
S. acinos L.	-	-	Triterpenes, oleanolic, ursolic, crataegolic acid, naringenin, rutinoside and eriodictyol	Escudero *et al*. (1985)
S. aintabensis	-	Antibacterial Antifungal	P-cymene	Azaz *et al*. (2005)
S. bachtiarica	Marzeh	Antibacterial	Carvacrol and *p*-cymene	Sefidkon *et al*. (2004)
S. boissieri Hausskn. ex Boiss.	-	Flavoring	Carvacrol, γ-terpinene and p-cymene	Kurkcuoglu *et al*. (2001)
S. boliviana Briq.	-	Antibacterial Antiviral	Γ-terpinene, β-caryophyllene and germacrene D	Laurent *et al*. (1997), Viturro *et al*. (2000)
S. brownei (SW.) Briq.	-	Antibacterial	Pulegone and menthone	Caceres *et al*. (1991), Rojas and Usubillaga (2000)
S. coerulea Janka	-	Antibacterial	Germacrene-D	Tumen *et al*. (1998)
S. cuneifolia Ten.	Wild savory or cuneate Turkish savory	Antibacterial Antidiabetes Carminative	Carvacrol, γ-terpinene, linalool and α-pinene	Aydn *et al*. (1995), Baydar *et al*. (2004)
S. douglasii (Benth.) Briq.	Douglas savory	-	Monoterpenes	Duke and Beckstorm-Sternberg (2001)
S. edmondi	Marzeh	Antibacterial	Carvacrol and thymol	Sefidkon *et al*. (2004)
S. forbesii (Benth.) Briq	-	Antioxidant	Geranial, neral	Ortet *et al*. (2009)
S. gilliesii	-	Antiprotozoal	Mono and sesquiterpene peroxides	Labbe *et al*. (1993)
S. glabella (Michx.) BRIQ.	Smooth savory	-	Germacrene D, isomethanol, menthone and limonene	Duke and Beckstorm-Sternberg (2001)
S. grandiflora L.	French savory	-	Germacrene D, isomethanone, pulegone and methanol	Duke and Beckstorm-Sternberg (2001)
S. hortensis L.	Summer savory	Analgestic Antibacterial Antifungal Antioxidant Antihyperglycemic Flavoring	Carvacrol, γ-terpinene, thymol and p-cymene	Hajhashemi *et al*. (2002), Zargari (1990) Gulluce *et al*. (2003), Sahin *et al*. (2003), Behravan *et al*. (2006), Mchedlishvili *et al*. (2005)

Table 1: Continued

Botanical and species	Local name	Therapeutic indications	Effective component	Reference
S. icarica P.H. Davis	-	Antibacterial	Carvacrol	Tumen *et al.* (2000)
S. intermedia C.A. Mey	-	-	Thymol, γ-terpinene and p-cymene	Sefidkon and Jamzad (2004)
S. khuzestanica jamzad.	-	Antibacterial Antidiabetes antioxidant Antihyperglycemic Antiinflammatory Antinociceptive	P-cymene and carvacrol	Haeri *et al.* (2006), Saadat *et al.* (2004)
S. kitaibelii Wierzb. ex Heuff.	-	-	p-cymene, geraniol and β-elemene	
S. macrantha C.A. Mey.	-	Antibacterial Antifungal	Carvacrol, p-cymene, limonene and thymol	Azaz *et al.* (2005), Sefidkon and Jamzad (2004)
S. montana L.	Winter savory	Antibacterial Antifungal Carminative Antioxidant Anticholinesterase Flavoring	Thymol, p-cymene, carvacrol, γ-terpinene, flavonoids, triterpenes	Oussalah *et al.* (2007), Mastelic and Jerkovic (2002)
S. mutica Fisch. and C. A. Mey.	-	Antibacterial Antimikotic	Carvacrol, thymol, γ-terpinene, p-cymene and methyl thymol	Behravan *et al.* (2004), Gohari *et al.* (2005), Sefidkon and Jamzad (2004), Sefidkon *et al.* (2004)
S. obovata Lag.	Iberian savory	Carminative	Flavonoids	Duke and Beckstorm-Sternberg (2001), Sanchez-de-Rojas *et al.* (1996)
S. parnassica Heldr. and Sart ex Boiss.	-	Antibacterial	Caryophyllene, carvacrol, caryophyllene oxide, spathulenol, p-cymene and linalool	Chorianopoulos *et al.* (2006), Tzakou and Skaltsa (2003)
S. parvifolia (Phil.) Epl.	Small-leaf Pampa savory	Analgestic Antibacterial Antifungal	Piperitone oxide	Duke and Beckstorm-Sternberg (2001), Viturro *et al.* (2000), Zygadlo and Grosso (1995)
S. pilosa Velen	-	Antibacterial	-	Tumen *et al.* (2000)
S. punctata	-	Antiprotozoal	Geranial, neral, alpha-bisabolol and (E)-nerolidol	Tariku *et al.* (2010)
S. sahendica Bornm.	-	Culinary herbs	Thymol, p-cymene and γ-terpinene	Sefidkon *et al.* (2004)
S. spicigera (C. Koch) Boiss.	-	Antibacterial	Thymol, p-cymene, γ -terpinene and carvacrol	Sefidkon and Jamzad (2004), Azaz *et al.* (2005), Eftekhar *et al.* (2009)
S. spinosa L.		Antibacterial	Monoterpene hydrocarbons and phenolic monoterpenes	Chorianopoulos *et al.* (2004)
S. subspicata Vis.	-	Antibacterial Antifungal	Carvacrol, α-pinene, p-cymene, γ-terpinene and thymol methyl ether	Skocibusic *et al.* (2008)
S. thymbra L.	Goat oregano	Antifungal Antiinflammatory Antinociceptive	Carvacrol and γ-terpinene	Glamoclija *et al.* (2006), Sokovic, *et al.* (2002)
S. wiedemanniana (Lallem.) Velen	-	Antibacterial	Carvacrol, thymol, p-cymene and γ-terpinene	Baser *et al.* (2001)

CONCLUSIONS

Clearly, herbal-based pharmaceuticals, cosmetics and flavoring are more welcoming every day. Numerous studies have been conducted to brighten both theoretical and practical aspects of the traditional usage of *Satureja* sp. There are remarkable varieties in chemical composition and therapeutic values of different species of this plant. In a recent investigation in Ethiopia, the oil of *S. punctata* contained 67 compounds of which geranial and neral were the main components with significant antiprotozoal activities (Tariku *et al.*, 2010). Similarly, these compounds were the major constituents of the essential oil of *S. forbesii* with potent antioxidant activity (Ortet *et al.*, 2009). Sefidkon *et al.* (2009) presented carvacrol and p-cymene as the most frequent component in *S. bachtiarica* oil while carvacrol and thymol were the most fluctuated elements in the oil of *S. mutica*. Their results showed the high antibacterial effect of these oils. Based on the conducted assessments so far, antibacterial, antifungal, antiviral, antioxidant, anti-diabetic, vasodilatory and analgesic activities are characterized as the most applicable properties of *Satureja* subspecies. In 2009 the inhibitory activity of acetyl- and butyrylcholinesterase by *S. montana* extracts was assessed as a potential indicator for the control of Alzheimer's disease. The result indicated a significant anticholinesterase activity of this species (Silva *et al.*, 2009).

According to the literature reviews, more than 90% of the present investigations only emphasized on the antibacterial activities of savory sp. while the other biological effects also seem promising. Monitoring and standardization is needed to direct studies passing through clinical trials. Various molecular, cellular and whole animal models should be used to demonstrate more valuable significance of *Satureja* sp. Future exploration are critical to assess the synergistic effects, efficacy and edibility of these essential oils.

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