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REVIEW ARTICLE

A Critical Overview on the Pharmacological and Clinical Aspects of Popular *Satureja* Species

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Abstract
Throughout the world, various parts of most *Satureja* species are traditionally used to treat patients with various diseases and complications. As for the presence of different classes of metabolites in *Satureja* and their numerous ethnomedical and ethnopharmacological applications, many species have been pharmacologically evaluated. The current work aimed to compile information from pharmacological studies on this savory for further investigations. The keyword *Satureja* was searched through Scopus and PubMed up to January 1, 2016. We found nearly 55 papers that dealt with the pharmacology of *Satureja*. We found that 13 species had been evaluated pharmacologically and that *Satureja khuzestanica*, *Satureja bachtiarica*, *Satureja montana* and *Satureja hortensis* appeared to be the most active, both clinically and phytopharmacologically. Regarding the content of rich essential oil, most evaluations were concerned with the antimicrobial properties. However, the antioxidant, antidiabetic and anticholesterolemic properties of the studied species were found to be good. In addition to the pharmacological activities that have been indentified for some species, opportunities still exist to assess the

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effectiveness of other well-known species. If different *Satureja* species are to have extensive ethnopharmacological applications, comprehensive assessments of the acute and chronic toxicities, as well as the teratogenicity, of those plants are needed.

1. Introduction

Almost 7000 species belonging to more than 230 genera are reported within the family Lamiaceae [1]. Among those genera, *Satureja* (savory) encompasses over 200 different herbs or shrub species that are often aromatic and are broadly found in the Mediterranean area, Asia and some parts of the US [2]. All over the world, flowers, leaves, stem and seeds of most of the *Satureja* species are traditionally used for various diseases and complications such as gastrointestinal cramps, nausea, diarrhea, muscle pains, and infectious diseases [3]. Because of the aromatic characteristics, leaves and aerial parts of this genus possess distinctive but pleasant tastes [4]. In Iran, *Satureja* is represented by 14 species in Flora Iranica, of which 11 have been reported [5].

Most of the savory species contain essential oil in their botanical parts. The yield of essential oil often exceeds 5% in different species of this genus [6]. With reference to the presence of monoterpenes such as thymol, carvacrol and cymene in the total essential oils [7,8], these metabolites resulted in the indication of antimicrobial activities against food, plants and human pathogens [9]. Flavonoids, tannins, acids and exudates are other known compounds in savory [6]. Based on the presence of all these metabolites, pharmacological properties such as antioxidant [10], anti-inflammatory and analgesic [11], and anti-hypercholesterolemic [12] activity have also been demonstrated.

Several species of savory are extensively and continuously used in ethnomedical and ethnopharmacological approaches of different cultures around the world. Valuable reports have been released on the pharmacological and clinical applications of this genus. Based on this, the current study aimed to compile and outline a frame from critical and pharmacological studies on this savory for further investigations.

2. Methods

To collect the data for this study, an extensive search with the keyword, *Satureja*, was carried out via two main search engines (Scopus and PubMed) from the beginning to January 1, 2016. All irrelevant papers as well as those on genetics, botany, agriculture, and chemistry were excluded. Almost 70 papers based on clinical and pharmacological aspects of different *Satureja* species were selected.

3. Results

3.1. Antimicrobial activities

Due to the rich amount of essential oils, different *Satureja* species have been assessed for possible antimicrobial activities. Using disc diffusion assay, the essential oil of *Satureja bachtiarica* demonstrated antibacterial activity against *Pseudomonas aeruginosa* as compared to erythromycin. Utilizing the broth dilution method, minimum inhibitory concentration (MIC) of *S. bachtiarica* essential oil was calculated as 31 μg/mL [13]. The ethanol extract of this species was assessed against some Gram-positive bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Streptococcus agalactiae*) and was found to be effective [14]. In another investigation using disc diffusion and agar dilution methods, the antimicrobial activity of the essential oils of this species against 10 clinical isolates of *Helicobacter pylori* was observed. The oil presented potent inhibitory effects against clinical isolates (17.6 ± 1.1 mm and 0.035 ± 0.13 μL/mL) [15].

Satureja calamintha is an Eastern Algerian species with antimicrobial activities. The essential oil of this plant has been evaluated against a wide range of microorganisms such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis* and *Streptococcus enterococcus*. MIC values of the concerned essential oil against those microorganisms were 20 μg/mL, 40 μg/mL, 80 μg/mL, 80 μg/mL, 40 μg/mL, 20 μg/mL, and 40 μg/mL, respectively [16]. The essential oil of this species was also effective against certain fungi (MIC = 2 μL/ml) [17].

The essential oil of *Satureja hortensis* has also been evaluated as an antimicrobial agent against various Gram-positive and Gram-negative microorganisms. The outcome of that study revealed the activity of the essential oil [18].

The essential oil of *Satureja intermedia*, an endemic species from Iran, has also been assessed for possible antimicrobial activities against different pathogenic bacteria and fungi such as *K. pneumoniae*, *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, and *Bacillus pumulis*, respectively. The oil was also active against *Candida albicans* and *Saccharomyces cerevisiae* (MICs were at the range of 47–12 mg/mL for bacteria and 7.5–1.75 mg/mL for fungi). Standard antibiotic and antifungal agents were ampicillin (10 μg/disc) and nystatine (30 μg/disc) in that study [19]. Another study revealed a considerable antimicrobial effect from *S. intermedia* essential oil against *Staphylococcus aureus* (MIC = 125 μg/mL) [20].

Three antimicrobial studies have been carried out on the essential oil and methanol of *Satureja khuzestanica*. Methanol extract of a native sample of *S. khuzestanica* demonstrated more active antimicrobial properties against *Staphylococcus aureus* and *Candida albicans* as compared to a cultivated sample [21]. Moreover, the antimicrobial activities of *S. khuzestanica* essential oil have been evaluated against a wide range of pathogenic bacteria and fungi [22]. In another investigation, *S. khuzestanica* essential oil containing carvacrol (90.8%) as the main constituent in full-

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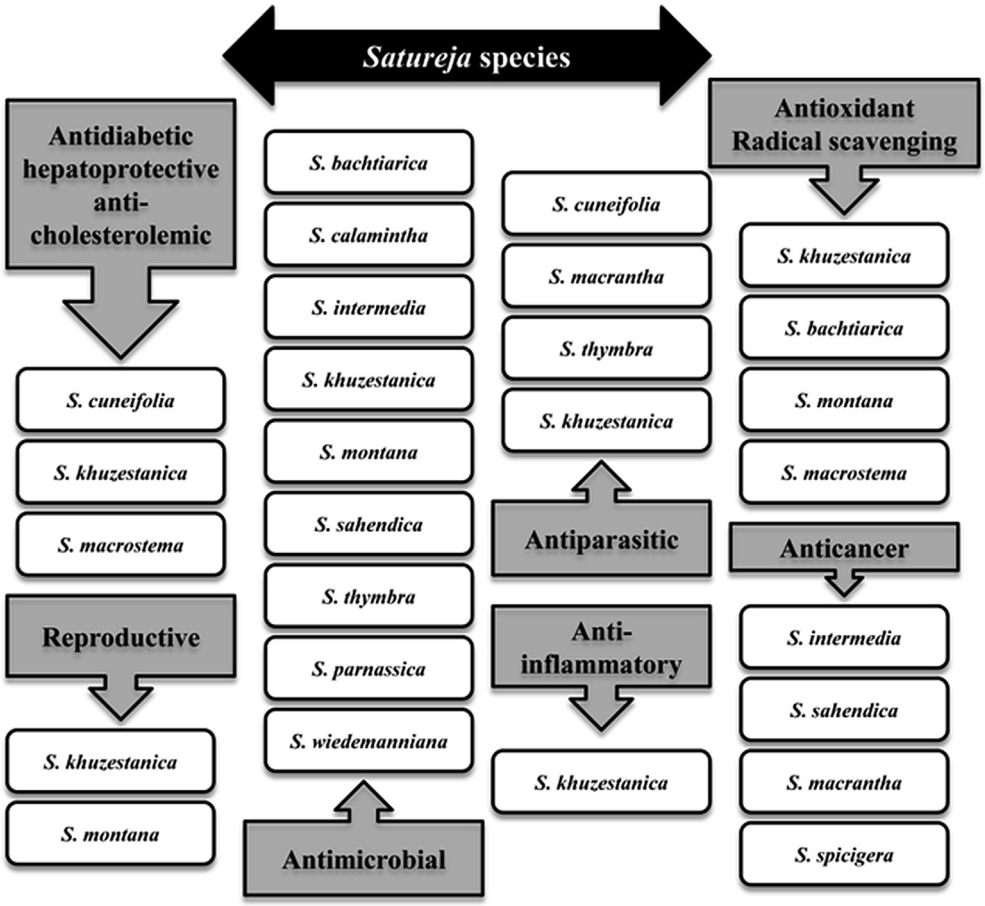

Figure 1 Different *Satureja* species and related proved properties.

flowering stage exerted maximum antimicrobial effects against studied pathogens as compared to other collection stages. MICs for pathogens sensitive to *S. khuzestanica* essential oil were in the range of 19—312 μg/mL [23]. The ethanol extract of *S. khuzestanica* fresh leaves were assessed for antifungal activity against some saprophytic fungi in comparison with amphotericin B by utilizing agar well diffusion method (MIC values in the range of 625—5000 μg/mL) [24]. Similarly, the hydroalcoholic extract of *S. khuzestanica* demonstrated antifungal activity against *Cryptococcus neoformans* isolates (MIC and minimal fungicidal concentration values in the range of 62.5—2000 μg/mL and 125—4000 μg/mL, respectively) [25].

Satureja kitaibelii is another medicinal species that has been evaluated for antimicrobial activities. The essential oil of this herb demonstrated potent activity (broth microdilution assay, MIC 0.97—15.6 mg/mL) when applied in a form of lozenge (0.2%). The MIC value for the essential oil was calculated as 0.10—25 μg/mL [26].

Using broth dilution method, minimum bactericidal concentration and MIC values for *Satureja montana* ethanol extract against *Staphylococcus aureus*, *Escherichia coli*, *Proteus morgani*, *Candida tropicalis* and *Trichophyton mentagrophytes* were determined at the range of 4.1—6.3% and 3.1—4.1%, respectively. In contrast, hole-plate diffusion method demonstrated the strongest activity of the aforementioned extract against *Bacillus subtilis*, *Sarcina flava*, *Candida tropicalis* and *Candida krusei* [27]. The antifungal activity of *S. montana* essential oil was studied against eight different fungi and two phytopathogens. Using a disc diffusion method, the maximum effectiveness of essential oil (carvacrol at around 60%) was demonstrated against *Trichophyton violaceum*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes* and *Pyricularia oryzae* (inhibition zone $>$ 70%) [28].

Satureja sahendica is another species with antibacterial activities. Disk diffusion method demonstrated that the essential oil containing thymol (40%), γ-terpinene (28%), and ρ-cymene (22%) possesses considerable antimicrobial activities on tested bacteria and fungi [29].

Another similar study on *Satureja thymbra* essential oil demonstrated the effectiveness of this species against different Gram-positive and Gram-negative strains [30], and some of those were multiple resistant. These sensitive strains were *Stenotrophomonas maltophilia* and *Chryseomonas luteola* [31].

A *Satureja* species from Mediterranean region, namely *Satureja parnassica* has been evaluated for possible antimicrobial activities. The extracted essential oil from this species was collected before flowering, just before flowering, full flowering, and after flowering periods. A comparative determination on samples revealed the maximum antimicrobial effects of the herb against *Salmonella enterica* and *Listeria monocytogenes* at full flowering period. The MIC values at two levels of bacterial inoculation (10^5 CFU/mL and 10^2 CFU/mL) on *Salmonella enterica* were

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64 μg/mL and 56 μg/mL on *Salmonella enterica* and 49 μg/mL and 35 μg/mL on *Listeria monocytogenes*, respectively [32].

Satureja wiedemanniana essential oil has been assessed for antibacterial effects against *Bacillus* species isolated from raw meat samples [33].

3.2. Antiparasitic effects

There is a report on the amebicidal activity of *Satureja cuneifolia* methanol extract (1.0–32.0 mg/mL) on *Acanthamoeba castellanii* cysts and trophozoites. The extract demonstrated both time- and dose-dependent amebistatic and amebicidal activities. No viable trophozoites were found within 24 hours in the presence of 32 mg/mL extract ($p < 0.05$) [34].

The trypanocidal activity of *Satureja macrantha* essential oil, diethyl ether extract and respective fractions on *Trypanosoma cruzi* epimastigotes was assessed in a study. *In vitro* trypanocidal assay resulted in minimum lethal concentrations of 12.5 μg/mL and 25 μg/mL for essential oil and diethyl ether extract, as compared to that of Gentian violet (positive control 6.25 μg/mL). Responsible constituents for such activity were found as thymol and carvacrol [35].

Satureja thymbra essential oil has been evaluated for acaricidal activity against field-collected unfed adult *Hyalomma marginatum* in an experimental study. The total volatile oil (5 μl/L, 10 μl/L, 20 μl/L, and 40 μl/L) as well as its major constituents, carvacrol (40 μl/L) and γ-terpinene (40 μl/L) were examined for possible tick mortality effect. Ticks exposed to vapors from cotton wicks with 40 μl/L produced 100% mortality in 3 hours. In contrast, only carvacrol and γ-terpinene produced knockdown in the evaluated species [36].

Hydroalcoholic extract of *S. khuzestanica*, an endemic species to Iran, has been examined against hydatid cyst protoscolices for possible scolicidal activity. The extract at the concentration of 1% was highly potent for in exposure time of 30 minutes, 1 hour and 2 hours. It was observed that by reducing the concentration or increasing the exposure time, mortality rate was reduced [37].

In a similar experimental assessment, scolicidal effects of *S. khuzestanica* essential oil were evaluated against protoscolices collected aseptically from hydatid cyst within affected sheep livers. The scolicidal effects of 3 mg/mL of the oil were found as 28.58%, 32.71%, 37.20% and 42.02% after 10 minutes, 20 minutes, 30 minutes, and 1 hour, respectively. Total scolicidal activity was found at 10 mg/mL after 10 minutes [38].

In another assessment, *S. khuzestanica* essential oil exerted antiparasitic activities against *Leishmania major* promastigotes inoculated in an animal model. In that study, the oil (0.01%) could reduce the progress of lesion size and decrease the mortality rate, as compared to the controls [39].

In addition to those studies on *S. khuzestanica*, the hydroalcoholic extract from their leaves demonstrated inhibitory activity against *Giardia lamblia* cysts, as compared to metronidazole. Fatality rate on cysts *in vitro* was determined as 32.52 ± 9.07% for the extract in comparison with that of metronidazole (28.75 ± 10.30%) [40].

3.3. Antiviral effects

Among *Satureja* species, it seems that only *S. montana* has been evaluated for antiviral activities (human immunodeficiency virus-1 induced cytopathogenicity in MT-4 cells). The aqueous extract of this plant exerted strong anti-human immunodeficiency virus-1 activity (effective dose = 16 μ/mL) against the virus and also respective reverse transcriptase [41].

3.4. Antioxidant and radical scavenging activities

With reference to high phenolic and flavonoid contents in *Satureja* species, different studies on the antioxidant and radical scavenging properties have been carried out on those species.

The methanol extract from two *S. bachtiarica* samples, wild and cultivated, has been assessed for those aforementioned activities through 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ferric ion reducing antioxidant power (FRAP) methods of assay. Higher levels of antioxidant and radical scavenging effect (29.04 mg/g and 58.25 mg/g Trolox via FRAP and DPPH, respectively) were observed for wild samples, which may be due to the higher phenolic compounds (24.50 mg caffeic acid/g sample) and total flavonoids (87.99 mg catechin/g sample) [42].

By using FRAP and thiobarbituric acid reactive substances (TBARS) assays, total antioxidant power and lipid peroxidation of *S. khuzestanica* essential oil were determined in rats. Regarding treatment with the essential oil, normal blood lipid peroxidation level was reduced (1.66 ± 0.25 nmol/mL treated with essential oil vs. 2.1 ± 0.33 nmol/mL untreated) and total antioxidant power was increased (98.25 ± 4.81 μmol/m treated with essential oil vs. 32 ± 2.86 μmol/m untreated) [43]. The essential oil extracted from *S. khuzestanica* also possessed antioxidant activities (225 mg/kg per day, orally) in reprotoxicity induced by cyclosporine in adult male Wistar rats. In that study, reduced sperm count, viability, fertilization, and blastocyst development rates were corrected via pretreatment with the essential oil [44]. Also in alloxan-induced type I diabetic rats, the essential oil of this species was assessed for possible antioxidant enzyme activity (500 ppm in drinking water). Following 8 weeks of intervention, serum level of glutathione, glutathione peroxidase serum activity, superoxide dismutase, and catalase in the essential oil group was increased, as compared to the controls [45].

With reference to antibacterial and antibiofilm activities against periodontopathogens, *S. hortensis* essential oil was evaluated for antioxidant properties in oxidative stress and excessive matrix metalloproteinase (MMP) expression/activity. Treatment with 1 μL/mL and 5 μL/mL of *S. hortensis* inhibited MMP activity and H_2O_2-induced cell death [46].

In an investigation, *Satureja macrostema* methanol extract was assessed for antioxidant properties through various antioxidant assays DPPH, superoxide, NO, hydroxyl radical scavenging, and iron-chelating activity. Compared to those of ascorbic acid (100 μg/mL), DPPH radical scavenging ability of the extract (100 mg/mL) was found in lesser amounts (89.87% vs. 97%). Compared to quercetin

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(50 μg/mL), the NO scavenging and superoxide anion of the extract (same amount) were not accepted (69.79 ± 4.17% and 66.12 ± 0.25% vs. 93.8 ± 0.98% and 90.87 ± 0.43%, respectively). In contrast, methanol extract showed highest activity on hydroxyl radical [50% inhibitory concentration (IC_{50}) = 49.65 μg/mL] [47].

Because of the presence of polyphenolic compounds, ethyl acetate fraction of *S. montana* methanol extract as well as the total essential oil demonstrated radical scavenging activity via DPPH assay [84.9% and 94.4% respectively as compared to Trolox, 98.2%, 50% effective concentration (EC_{50}) = 44 ± 1.63 μg/mL and 128 ± 2.26 μg/mL, respectively) [48]. In a similar study, DPPH assay and 2, 2'-azinobis (3-ethylbenzothiazoline-6-sulphonic acid method (ABTS) on *S. montana* methanol extract resulted in EC_{50} values of 116.36 ± 12.83 μg/mL and 106.59 ± 1.41 μmol Trolox equivalents/g dry sample, respectively [49].

The spray-dried hydroalcoholic extract of *S. montana* in combination with 10% maltodextrin as carrier and drying agent resulted in a potent radical scavenging activity (IC_{50} = 5.24 μg/mL) via DPPH assay [50].

The antioxidant effects of *S. hortensis* essential oil on safflower oil oxidation has been studied through different related methods, such as DPPH, ABTS, ferric thiocyanate, and β-carotene bleaching. The oils exerted considerable activities in different concentrations [51]. A similar study on the hydroalcoholic extract of this plant revealed positive antioxidant and radical scavenging activities ($IC_{50\ DPPH} < 300$ μg/mL) [52]. Another study demonstrated that both essential oil (1 μL/mL and 2.5 μL/mL) and ethanol extract (2.5 mg/mL) of *S. hortensis* may decrease the rat lymphocytes oxidative damage induced by hydrogen peroxide [53].

3.5. Anti-inflammatory, antinociceptive and healing activities

Essential oil, hydroalcoholic and polyphenolic extracts of *S. hortensis* seeds have been evaluated for possible anti-inflammatory and analgesic activities. Acetic acid and formalin (analgesic methods) and carrageenan-induced rat paw edema (anti-inflammatory) tests were used. In that study, pretreatment with those extracts decreased acetic-acid-induced abdominal twitches and paw edema [54]. Another investigation demonstrated that an aqueous extract of this herb (200 mg/kg) could diminish the morphine withdrawal syndrome signs [55]. A similar study revealed that both hydroalcoholic and essential oil of this plant could inhibit the mice writhing responses caused by acetic acid [56]. To assess the therapeutic effects of *S. hortensis* in periodontal inflammation, a study revealed that the herb essential oil can reduce the ratio of live/dead bacteria and increase the membrane permeability [57].

Satureja horvatii essential oil has demonstrated antimicrobial effects against certain bacteria (MIC 0.03–0.57 mg/mL) and yeast strains (MIC 0.56–2.23 mg/mL) [58].

S. khuzestanica has been studied for analgesic and anti-inflammatory activities. The hydroalcoholic extract of *S. khuzestanica* has been evaluated for anti-inflammatory and antinociceptive effects by means of carrageenan-induced rat paw edema and formalin test, respectively. The extract [150 mg/kg; intraperitoneally (i.p.)] was as effective as indomethacin (4 mg/kg; i.p.) based on anti-inflammatory activities. The antinociceptive effect was found to be dose-dependent (10–150 mg/kg; i.p.) as compared to morphine (3 mg/kg; i.p.) [11]. Another study confirmed the antinociceptive activities of *S. khuzestanica* ethanol extract utilizing different tests such as tail-flick, hot-plate, and acetic acid (writhing test). Regarding tail-flick and hot-plate tests, the extract (100 mg/kg; i.p.) demonstrated analgesic effect at 15 minutes following the injection and peak at about 30 minutes after injection. The effect was permanent for almost 45 minutes. Through the acid acetic test, the extract demonstrated the effectiveness at 100 mg/kg and 150 mg/kg [59].

In another investigation, it was observed that *S. khuzestanica* (25 mg/kg, 50 mg/kg, and 100 mg/kg, i.p., simultaneously with morphine) may dose-dependently have preventive effects on opioid analgesic tolerance in adult male Wistar rats. The outcomes were of significant increase in glial fibrillary acidic protein and tumor necrosis factor α levels, which were reversed to control levels when subjected to 100 mg/kg of the extract [60].

Furthermore, it has been revealed that *S. khuzestanica* possess protective effects in patients with recurrent aphthous stomatitis. In a placebo-controlled randomized clinical trial, both *S. khuzestanica* essential oil (Group A) and hydroalcoholic extract (Group B) were evaluated in comparison with a hydroalcoholic solution as placebo. Mean time of pain elimination in both *S. khuzestanica* groups showed significant differences as compared to placebo (3.40 ± 0.50 days and 3.20 ± 0.41 days for *S. khuzestanica* groups vs. 5.70 ± 1.12 days) in the placebo group. The mean duration of complete healing in *S. khuzestanica* groups (5.90 ± 1.24 days and 6.85 ± 1.30 days) were also significantly different from that of the placebo (10.40 ± 1.66 days) [61].

Compared to prednisolone as the standard drug, *S. khuzestanica* essential oil was evaluated for possible effectiveness against acetic-acid-induced inflammatory bowel disease in a mouse model. According to the outcomes of that study, lipid peroxidation, a marker for evaluating oxidative stress, was restored in prednisolone and essential oil groups (500 ppm, 1000 ppm, and 1500 ppm). In contrast, myeloperoxidase activity was significantly reduced with both 1000 ppm and 1500 ppm of the oil as well as prednisolone. Furthermore, score values of macroscopic and microscopic characters were reduced in essential oil (1000 ppm and 1500 ppm) and prednisolone groups [62].

3.6. Antidiabetic, hepatoprotective, anticholesterolemic and allied activities

Via an animal study, it was concluded that administration of *S. cuneifolia* tea (80 mg/kg) to the affected rats may have antihypercholesterolemic effects as compared to the control and cholesterol groups (2% cholesterol-containing pellet feed) [63].

The different preparations of *S. khuzestanica* have been assessed for possible antidiabetic, hypoglycemic and antihyperlipidemic activities. In an assessment, S.

khuzestanica essential oil significantly decrease the level of glucose (258 ± 18.1 mg/dL vs. 325 ± 21.5 mg/dL in the control group), total cholesterol (146 ± 9.6 mg/dL vs. 156 ± 14.1 mg/dL in the control group) and triglyceride (166 ± 14.9 mg/dL vs. 201 ± 17.6 mg/dL in the control group) in streptozocin-induced diabetic rats as well as those rats receiving a lipid regimen [43]. In a similar study on alloxan-induced type I diabetic rats, the oil significantly inhibited the activities of liver enzymes and decrease fasting blood glucose, triglyceride, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) [64].

Another investigation on serum glucose levels and lipid profile in male streptozotocin-induced diabetic rats revealed that *S. khuzestanica* ethanol extract (100 mg/kg) could significantly reduce the LDL, VLDL, and triglyceride levels. Moreover, doses of 100 mg/kg and 300 mg/kg of the extract reduced the fasting blood sugar after 1 month of administration [65].

Regarding the association of liver in body glucose metabolism, a study demonstrated that *S. khuzestanica* essential oil (1000 ppm added to drinking water of rats for 2 weeks) could alter the key enzymes of glycogenolysis and gluconeogenesis, glycogen phosphorylase (24% increased) and phosphoenol pyruvate carboxy kinase (26% decreased), as compared to controls. Nevertheless, the oil had no impact on blood sugar concentrations [66].

S. khuzestanica has been traditionally accepted as a liver tonic herb. It has been proven that hyperthyroidism is often associated with liver oxidative stress and thus may lead to liver dysfunction. Accordingly, *S. khuzestanica* essential oil was investigated for possible hepatoprotective activities in hyperthyroid rats. The oil (225 mg/kg) was effective on serum aspartate transaminase, alanine transaminase, and hepatic malondialdehyde when administered in combination with vitamin E (200 mg/kg) [67].

In a double-blinded randomized controlled trial on patients with type II diabetes mellitus, *S. khuzestanica* crude leaves powder (250 mg/day for 2 months) was assessed for possible effectiveness on some metabolic parameters. Treatment of patients with crude leaves powder revealed significant decrease in total cholesterol and LDL levels as well as increase in high-density lipoprotein-cholesterol, total antioxidant power, and TBARS. On the contrary, the plant exhibited no impacts on serum glucose level, triglyceride, creatinine, and TBARS [68]. Despite the positive results on the antidiabetic activities of *S. khuzestanica* in animal models, outcomes of this study showed that the antidiabetic activities of this plant in human have not yet been confirmed [69].

S. khuzestanica essential oil could significantly ameliorate the progress of diabetic nephropathy in alloxan-induced diabetic rats as compared to control and diabetic untreated groups. The oil (250 ppm or 500 ppm added to drinking water for 8 weeks) inhibited the progression of glomerular hypertrophy, glomerulosclerosis, glomerular number loss, lipid peroxidation, serum creatinine, and urea in comparison with diabetic untreated group [70].

Methanol extract of *S. macrostema* possessed hepatoprotective activity as it could ameliorate lipid peroxidation in carbon tetrachloride and paracetamol-induced hepatic damaged rats [47].

Using a standard method [71], the spray-dried hydro-alcoholic extract of *S. montana* in combination with different concentrations of maltodextrin as carriers was evaluated experimentally for possible angiotensin-I-converting enzyme (ACE) inhibition activity. The extract in three samples (associated maltodextrin as 10%, 30% and 50%) exhibited similar ACE inhibition (IC_{50} values of 0.33 mg, 0.33 mg, and 0.49 mg, respectively) [50].

3.7. Anticancer and cytotoxic effects

Using MTT (3-[4, 5-dimethylthiazol-2-yl]-2, 5 diphenyltetrazolium bromide) assay, cytotoxic activities of *S. intermedia* essential oil were assessed on two human cancerous cells (esophageal squamous cell carcinoma and human bladder carcinoma cell lines). The results revealed a considerable activity ranging from 39 μg/mL to 1000 μg/mL (IC_{50} = 156 μg/mL) [19].

Using brine shrimp lethality assay (BSLA), diethyl ether, methanol, and water extracts of *S. macrantha* as well as column chromatography-isolated terpenoids were evaluated for possible cytotoxic activity against water life brand brine shrimp (*Artemia salina*) eggs. Seawater and a well-known cytotoxic alkaloid, berberine hydrochloride (LC_{50} = 26 μM) were selected as controls. Results from BSLA showed that three isolates especially oleanolic acid (LC_{50} = 17 μM) were effective [72].

Brine shrimp lethality as well as four cancerous cell lines, HT29/219, Caco2, NIH-3T3, and T47D (human breast ductal carcinoma) were selected to evaluate the possible cytotoxic activities of isolated chalcone and flavanones from aerial parts of *Satureja spicigera*. Among those isolates, 5, 7, 3′, 5′-tetrahydroxy flavanone and 5,4′-dihydroxy-3′-methoxyflavanone-7-(6″-O-α-L-rhamnopyranosyl)-β-D-glucopyranoside were effective against *Artemia salina* larva (LC_{50} = 2 μg/mL) and T47D (IC_{50} = 98.7 μg/mL), respectively. The controls were seawater and berberine hydrochloride (LC_{50} = 26 μM) and the methods were BSLA and MTT cytotoxicity assays [73].

MTT cytotoxicity assay was used to evaluate the *S. sahendica* essential oil cytotoxic activities against human cancer cell lines. According to the outcomes of that study, cell viability of MCF7, Vero, SW480 and JET 3 cancerous cells (IC_{50} values were calculated as 15.6 μg/mL, 15.6 μg/mL, 125 μg/mL, and 250 μg/mL, respectively) were significantly reduced dose-dependently [29].

3.8. Cardiovascular effects

The inhibitory effects of *S. hortensis* methanol extracts on adhesion of the activated human platelet to laminin-coated plates as well as aggregation and protein secretion were assessed. The extract could inhibit the platelet adhesion to laminin-coated wells by 48% [74].

3.9. Diuretic activity

The extracted essential oil of *S. montana* has demonstrated diuretic activity in an animal model when compared with an infusion and water–alcohol extract. Nevertheless, both

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essential oil (0.1%) and infusion (10%) solutions were effective in 3 days of experimentation [75].

3.10. Fertility effects

S. khuzestanica essential oil (75 mg/kg per day, 150 mg/kg per day, and 225 mg/kg per day for 45 days in drinking water) was revealed to have positive male fertility effects in male rates. With reference to the outcomes, potency, fecundity, fertility index, and litter size as well as testosterone level, weights of testes, seminal vesicles were significantly improved. Higher doses (150 mg/kg and 225 mg/kg) of the oil could also increase the number of spermatogonia and spermatozoids [76].

In an animal study, the improvement effects of *S. montana* hydroalcoholic extract on premature ejaculation and copulatory behavior in rats were examined. The extract was orally administered for eight consecutive days (25 mg/kg and 50 mg/kg). In comparison to control, acute administration of the extract in both doses as well as subacute use of the extract at lower dose resulted in a significant increase in ejaculation. In addition, the extract could decrease the intromission frequency with the same administration condition. In addition, testosterone serum level in rats acutely treated with 50 mg/kg of the extract was significantly elevated as compared to that of the control [77].

3.11. Gastrointestinal activities

S. hortensis essential oil was assessed for antispasmodic activity on contractions of isolated ileum compared with the effect of atropine and dicyclomine. The oil (0.1 mL/100 g) could also inhibit castor-oil-induced diarrhea in mice [78]. Another species, *Satureja obovata* has also been evaluated for possible spasmolytic effects against acetylcholine. Total terpene content of this essential oil was responsible for the studied activity [79].

3.12. Immunostimulant effects

The effect of *S. bachtiarica* ethanol extract (200 mg/kg and 400 mg/kg) on immunological parameters in Wistar rats was assessed. The extract demonstrated a significant increase in albumin levels (200 mg/kg), phagocytosis number (400 mg/kg) and neutrophil count (400 mg/kg). Accordingly, the herb can be introduced as an immunostimulant without causing hematological side effects [80]. Solely and in combination with another medicinal herb, the effectiveness of *S. khuzestanica* on lysozyme activity and hematological factors was assessed in common carp. Serum lysozyme activities were significantly different in various treatments. *S. khuzestanica*, in both conditions, increased the resistance of common carp [81].

3.13. Respiratory-related activities

Different concentrations of *S. hortensis* hydroalcoholic extract have been evaluated for their relaxant effect on guinea pig trachea. Compared to theophylline, the plant demonstrated a potent activity in higher concentrations [82]. The aqueous extract (250 mg/kg) of *S. hortensis* could exert anti-inflammatory effects on induced rhinosinusitis in rabbits. Topical application of this extract could decrease both NO synthase enzyme and concentration of NO radical metabolites [83].

3.14. Other pharmacological properties

In an investigation on *Satureja viminea*, hippocratic screening showed that the respective aqueous extract (500 mg/kg and 1000 mg/kg) decreased the motor activity of nonfasted Sprague—Dawley female rats. In contrast, doses of 500 mg/kg and 750 mg/kg of *S. viminea* essential oil produced a higher decrease in motor activity. To assess the exploratory behavior and curiosity of animals under oral administration of *S. viminea* essential oil, 1000 mg/kg of the oil significantly reduced the numbers of holes (from 60 ± 2.6 to 2.2 ± 1.1) explored by albino mice, as compared to that of the vehicle (from 61 ± 4.2 to 43 ± 7.5). These two tests simply showed the sedative effects of *S. viminea* [84].

The protective effects of *S. montana* hydroalcoholic extract were evaluated against cyclophosphamide-induced testicular damage in rats. The extract was administered orally (50 mg/kg per day) for 7 days before and after cyclophosphamide injection (200 mg/kg i.p.). The extract could restore and increase the relative testicular weight, serum testosterone level, and alkaline phosphatase activity as well as testicular acid phosphatase and sorbitol dehydrogenase activities. Improving the total antioxidant capacity, the extract could also reduce the lipid peroxidation. In contrast, testicular DNA fragmentation was mitigated in the extract group. The protective effects of the extract were also confirmed by histopathological assessments. Antiapoptotic and antioxidant activities were mentioned as main mechanisms of the extract in that study [85].

3.15. Toxicity

An animal study demonstrated that application of *S. cuneifolia* (80 mg/kg) could be responsible for granular degeneration in the liver of Wistar albino rats [63].

4. Conclusions and future perspectives

The current study aimed to compile studies carried out pharmacological activities of most popular *Satureja* species. According to the outcomes, most of the performed studies focused on the antibacterial and antifungal activities that are closely related to the presence of rich monoterpenes in those species [86]. Nevertheless, antiviral effects of the mentioned species should be given consideration. Among those species, the anti-inflammatory and analgesic activities, mostly related to *S. khuzestanica*, were found. In this regard, it could be interesting to study the respective properties on other well-known species. In addition to these findings, there was only one study on the possible toxicity of a certain *Satureja* species (*S. cuneifolia*). Regarding the extensive ethnopharmacological application of different *Satureja* species, comprehensive assessments on acute and chronic toxicity as well as

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teratogenicity of those medicinal plants are recommended (Fig. 1).

Disclosure statement

Authors of this manuscript have no conflicts of interest.

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