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Review

A review on *Hyssopus officinalis* L.: Composition and biological activities

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***Hyssopus officinalis* L. (Hyssop) is one of the most popular herbal preparations, mainly distributed in the East Mediterranean to central Asia. The plant has been used traditionally for medicinal purposes; generally, these therapeutic uses and health benefits of hyssop are largely based on folklore rather than on scientific substantiation, making it a good candidate to gather documentations, including the phytochemical content, *in vitro* experiments, animal models and human studies available in the recent scientific studies. A literature review on the chemical and biological aspects of the plant indicates that the main constituents of *H. officinalis* include several polyphenolic compounds, primarily the flavonoids apigenin, quercetin, diosmin, luteolin and their glucosides followed by other phenolic compounds chlorogenic, protocatechuic, ferulic, syringic, p-hydroxybenzoic and caffeic acids. Reports on the essential oils extracted from aerial parts of *H. officinalis* revealed several principal components, including terpenoids pinocamphone, isopinocamphone and β-pinene. Hyssop has moderate antioxidant and antimicrobial activity against Gram positive and negative bacteria activities together with antifungal and insecticidal antiviral properties *in vitro*. Animal model studies indicate myorelaxant, antiplatelet and α-glucosidase inhibitory activities for this plant. However, human studies, adverse reactions and clinical trials examining the reported properties of hyssop are absent and needs more attention to determine whether biological differences in findings of the studies reflect the different isolation procedures, different types of plant material used, collection time, locations or different chemotypes.**

Key words: *Hyssopus officinalis* L., phenolic compounds, essential oil, extract.

INTRODUCTION

One of the most frequently consumed herbal remedies available today is the hyssop preparations prepared from *Hyssopus officinalis* (L) which is gaining increased importance as a minty flavor, condiment and spices in food industries as well (Dragland et al., 2003; Jung et al., 2004; Lugasi et al., 2006). Not surprisingly, like many other herbal preparations used in traditional medicinal cultures, the therapeutic uses and health benefits of hyssop are largely based on folklore rather than on scientific substantiation. Regardless of the wide range of literatures suggesting health benefits of herbal remedies associated with hyssop, evidence-based information regarding the effects of hyssop is quite limited. Developing an efficient herbal remedy is reliant to a better understanding of the relationship between chemical constituents and biological properties of the natural product. In view of these aspects, natural products, particularly higher plant species, continue to be important sources of medicine and supplementary health products which represent a challenge to science due to their various properties, including chemical diversity, synergism to biological activity and variable compositions. Herein, we tried to gather detailed documentations of the available scientific papers related to the bioactivity and potential health benefits of hyssop ensuring a high quality herbal medicine to meet the ever more demands of the public.

NOMENCLATURE

The genus *Hyssopus* comprises aromatic perennial herbs or subshrubs that are mainly cultivated, but can also be

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found in the wild. The inflorescence is 20 to 25 cm long, false spikelike, composed of 4 to 10 flowered pseudoverticils in the terminal. The root of *H. officinalis* is a strongly branching, multi-headed tap root. The stems are 0.5 to 0.7 m in height, erect or decumbent dividing into many woody stems. The leaves are opposite, shiny dark-green, entire-edged and lanceolate or oblong, obtuse to acuminate that are 2 to 4 cm long and 0.5 to 1 cm wide. *Hyssopus* L. comprises of about 10 to 12 species distributed mainly in the East Mediterranean to central Asia. *H. officinalis* L. (Family: Lamiaceae alt. Labiatae) has a long history of medicinal use as carminative, tonic, antiseptic, expectorant and cough reliever. Despite having a slightly bitter taste, *H. officinalis* is often used as a minty flavor and condiment in food industries. The merit of the traditional use of *H. officinalis* has been supported by some prior studies from the genus *Hyssopus*, providing several biologically active constituents especially main compounds from essential oils. Although, a great body of papers refers to the composition of *H. officinalis* oil, far too little attention has been paid to the chemical constituent structures present in the plant. Herein, we offer documentations including the phytochemical content, *in vitro* experiments, animal models and human studies available in the recent scientific literatures.

PHYTOCHEMICAL CONSTITUENTS

The phytochemical study of the aerial parts of *H. officinalis* cultivated in Xinjiang, China, revealed isolation of two new flavonoid glycosides and nine other known flavonoids from the ethanolic extract of the plant. The new compounds were identified as; quercetin 7-O-b-D-apiofuranosyl-(1→2)-b-dxylopyranoside (1) and quercetin 7-O-b-D-apiofuranosyl-(1→2)-b-D-xylopyranoside 30-O-b-D-glucopyranoside (2), together with nine known flavonoids apigenin (3), apigenin 7-O-b-D-glucopyranoside (4), apigenin 7-O-b-D-glucuronopyranoside methyl ester (5), luteolin (6), apigenin 7-O-b-D-glucuronide (7), apigenin 7-O-b-D-glucuronopyranoside butyl ester (8), luteolin 7-O-b-D-glucopyranosid (9), diosmin (10) and acacetin 7-O-a-L-rhamnopyranosyl-(1→6)-b-D-glucopyranoside (11). The free radical scavenging activity of the compounds 1 to 11 was also determined using 2,2-diphenyl-1-picrylhydrazyl (DPPH). The isolated compounds were found to possess noble radical scavenging activity. Out of the isolated compounds, 1, 2, 6 and 9 with IC50 values in the range of 2.81 to 10.41 mmol/L exhibited stronger scavenging activity on DPPH assay than butylated hydroxytoluene and L-ascorbic acid as standards (Wang and Yang, 2010).

Mario et al. (1997) revealed the presence of the most widespread class of secondary metabolites, flavonoids, in *H. officinalis* L. using high-performance liquid chromatography and magnetic-resonance imaging (NMR) spectroscopy. The major flavone, diosmin, was present in the plant with 51 and 40.5% in sepals and leaves, respectively that were identified as the total content of diosmin in whole plant. Nonetheless, there were changes in diosmin levels during the development of hyssop leaves, stems and roots. The other identified compound in the plant was considered to be isoferulyl D-glucose ester (Marin et al., 1998). Previously, Hilal et al. (1979) reported isolation of seven glycosides of flavanone type from *H. officinalis* where the aglycon of the glycosides were determined as 5,4'-dihydroxy-7,3'-dimethoxy flavanone.

The content of free phenolic acids (PhAs) for ten popular medicinal plants used in Polish phytotherapy including *H. officinalis* belonging to the family Lamiaceae were determined by a rapid, selective and accurate extraction method combining solid-phase extraction and high-performance liquid chromatography. Considering the findings of the study, methanolic extract of the *H. officinalis* was shown to be rich in phenolic compounds, especially high in chlorogenic, protocatechuic, ferulic, syringic, p-hydroxybenzoic and caffeic acids followed by vanillic, p-coumaric, rosmarinic and gentisic acids (Murakami et al., 1998; Varga et al., 1998a; Kochan et al., 1999; Zgorka and Głowniak, 2001). Elsewhere, the presence of caffeic acid and its derivatives in the roots of *H. officinalis* L. cultivated in Romania with a content of 1.69% was reported. Additionally, rosmarinic acid, ferulic acid and phenylpropanic compounds were also identified in the plant by chromatography and spectrophotometric analyses (Benedec et al., 2002). Later, Proestos et al. (2005) employed reversed phase high-performance liquid chromatography with UV detection for the identification and quantification of the phenolic compounds for some plant extracts including *H. officinalis*. The most abundant phenolic acids in *H. officinalis* were considered to be ferulic acid (13.2 mg/100 g of dry sample) and caffeic acid (6.5 mg/100 g of dry sample). Moreover, syringic, gentisic and p-hydroxybenzoic acids along with two flavonoids (+)-catechin and apigenin were also detected in the genus *H. officinalis* (Proestos et al., 2005).

ESSENTIAL OIL

Garg et al. (1999) reported on the characteristics of the oil of *H. officinalis* L. *ssp. officinalis* cultivated in the North Indian plains as an annual crop. The GC and GC-MS analysis of the colourless essential oil led to the identification of 21 compounds representing 95.6% of the oil, comprising seven monoterpene hydrocarbons (32.3%), five oxygenated monoterpenes (60.5%), one phenol (0.2%) and six sesquiterpene hydrocarbons (0.35%). The major constituents of the camphorous predominant monoterpenes of the oil were pinocamphone (49.1%) >β-pinene (18.4%)

>isopinocamphone (9.7%) (Shah et al., 1986; Garg et al., 1999). Myrtenol methyl ether, myrtenic acid, methyl myrtenate, pinic acid, cis-pinic acid, (+)-2-hydroxyisopinocamphone, pinonic acid and cis-pinonic acid were identified for the first time in *H. officinalis* oil by Joulain (Joulain, 1976; Joulain and Ragault, 1976). The analysis of the composition of two essential oils from *H. officinalis L.* ssp. *officinalis* grown in two different localities near Urbino (Marche, Italy) revealed major essential oil components as pinocamphone (34 and 18.5%), isopinocamphone (3.2 and 29%) and β-pinene (10.5 and 10.8%). However, they showed detectable differences in the ratio of pinocamphone/isopinocamphone and in the percentage of linalool (0.2 and 7.9%) and camphor (0.3 and 5.3%). All the same, the essential oils exhibited antifungal activity against 13 strains of phytopathogenic fungi; the essential oil of the plants grown at 1000 m above sea level was superior (Daniele et al., 2004). Another study performed with the *H. officinalis* from U.P. Himalaya explained the presence of isopinocamphone 38.1%, pinocarvone 20.3%, 1-8-cineole 12.2% and β-pinene 10.2% as the main compounds and the total 47 chemical constituents represented 98.56% of the total oil (Shah, 1991). Salma et al. (2002) identified *H. officinalis* as a new source of essential oil in Egypt that was characterized by high content of β-pinene (19.60%), pinocamphone (19.20%) and camphor (16.3%). The highest yield of oil production was determined at the flowering stage of growth, in July (Salma et al., 2002). Bulgarian and Italian essential oils of *H. officinalis L.* were analyzed and the main difference between these two kinds of hyssop oils was in the higher quantity of terpenoids in Bulgarian oil. Isopinocamphone and its biogenetic precursor β-pinene, camphor, 1,8-cineole, cubenene and germacrene B were detected in the Bulgarian oil, whereas in the case of Italian hyssop oil, β-pinene was the minor component and phenyl propanoids, safrole and benzyl benzoates, were the predominant constituents of the oil (Manitto et al., 2004). Garcia-Vallejo et al. (1995) examined the volatile oil of *H. officinalis* grown in Spain by gas chromatography (GC) and gas chromatography/mass spectrometry (GC/MS) and reported a high content of 1,8-cineole (52.89%) and β-pinene (16.82%) as the main components of the oil. In another study, Özer et al. (2005) analyzed the essential oil of *Hyssopus officinalis L. subsp. angustifolius* (Bieb.) Arcangeli wild-growing in the Eastern Anatolian region of Turkey. The essential oil of this plant demonstrated the presence of many monoterpenes that were identified by gas chromatography; about thirty-four components were characterized, representing 91.0% of the total components detected. The main components were identified as pinocarvone (36.3%), pinocamphone (19.6%), β-pinene (10.6%), 1,8-cineole (7.2%) and isopinocamphone (5.3%) (Hold and Sirisoma, 2002; Ozer et al., 2005). Salvatore et al. (1997) performed detailed examination of the essential oil of *H. officinalis* L. *var. decumbens* from the High-Provence Alps in Banon, France. Linalool (49.6%), 1,8-cineole (13.3%), limonene (5.4%), β-caryophyllene (2.8%), β-pinene (3.0%) and α-pinene (2.4%) were identified as the major components of the essential oil, while iso-pinocamphone and pinocamphone were present at a lower content level suggesting the existence of different chemotypes in that province (Salvatore et al., 1997). Analysis of the essential oils of *H. officinalis* L. *var. decumbens* (HOD) from France (Banon) and *H. officinalis* (HO) from Italy by GC and GC/MS exhibited notable differences in the amounts of components. The bicyclic monoterpene ketones, pinocamphone and isopinocamphone, were present in HO, but their percentages were very low in HOD, where instead linalool (49.6%), 1,8-cineole (13.3%) and limonene (5.4%) were predominant (Salvatore et al., 1998). Chemical analysis for three essential oils of endemic *H. officinalis* cultivated in Yugoslavia: *f. albus Alef., f. cyaneus Alef.* and *f. ruber Mill.* showed that components mainly composed of cis- and trans-pinocamphone and pinocarvone, together with lesser amounts of germacrene D, bicyclogermacrene, elemol and spathulenol (Chalchat et al., 2001). Furthermore, the presence of aliphatic fatty acids, such as palmitic acid 15.60%, stearic acid 10.73%, linolenic acid 63.98%, arachidic acid 2.64% and eicosadienoic acid 0.68% in the Romanian hyssop oil was determined (Benedec et al., 2002). In our previous study for the essential oil from Iran, the main constituents were myrtenyl acetate (74.08%), camphor (6.76%), germacrene (3.39%), spathulenol (2.14%), caryophyllen oxide (2.13%) and β-caryophyllene (2.10%) with lesser amounts of cis-sabinol (1.75%), β- bourbonene (1.47%) and bornyl acetate (1.42%) (Fathiazad et al., 2011).

Kerrola et al. (1994) investigated the volatile compounds of the four phenotypes of *H. officinalis* L. differentiated by the color of the corolla, by Soxhlet extraction and Supercritical Fluid Extraction (SFE). The main components of all extracts were identified as pinocamphone, isopinocamphone, and pinocarvone. However, differences in the quantity of the constituents were worth mentioning; the lower amount of monoterpene hydrocarbons and a higher amount of oxygenated hydrocarbons were obtained in the SFE (Kerrola et al., 1994). Detailed examination of the SFE of the hyssop oil was undertaken by Kazazi et al. (2007) at various pressures, temperatures, extraction (dynamic and static), times and modifier (methanol) concentrations. Considering the impacts of different factors during the extraction, it was shown that the composition of the extracted oils was significantly influenced by the operating conditions. Major components of the extracts under different SFE conditions were sabinene (4.2 to 17.1%, w/w), iso-pinocamphene (0.9 to 16.5%) and pinocamphene (0.7 to 13.6%). Consequently, SFE offered more choices with parameters for the extraction

of different components of the hyssop oil (Kazazi et al., 2007). Kazazi and Rezaei (2007) in another study evaluated effects of various parameters on the selective extraction of compounds from hyssop using SFE and hydrodistillation. Sabinene, pinocamphene and iso-pinocamphene were the major compounds applying SFE with different operational conditions. The optimized conditions of SFE for the highest extraction selectivity of pinocamphene and iso-pinocamphene were achieved at 100 atmosphere, 45°C temperature, with 4.5 µl (0.14%, w/w) methanol, dynamic extraction time of 20 min and static extraction time of 25 min. Nonetheless, the results of the study suggested that the hyssop collected from Iran could be a special chemotype with a high sabinene concentration (11.04%) (Kazazi and Rezaei, 2009). More recently, Langa et al. (2009) studied the effects of pressure, temperature and flow rate of CO_2, as well as the particle size of the vegetable material, on the yield and composition of the SFE of essential oil from *H. officinalis* in comparison with HD extraction. The major compounds for both techniques were 1,8-cineol (eucalyptol) (60 to 75%) followed by terpinen-4-ol (4 to 10%), pinocarvone (2 to 6%) and β-pinene (1 to 6%). In spite of the major similar compounds with comparable oil yields for both SFE and HD methods, heavier compounds were detected for the oil obtained from SFE technique (Toth et al., 1989; Langa et al., 2009).

On the whole, the essential oil content may vary considerably within a single species from one growth season to another, affected by extraction method, climatic parameters and agrotechnical factors (Benhammou et al., 2008; Ghalem and Mohamed, 2009; Xu et al., 2011). Additionally, many plants have various chemotypes that differ in their both quantitative and qualitative diversity in the composition of essential oils obtained (Varga et al., 1998b). Further studies are mandatory to determine the origin of the differences observed during examinations.

IN VITRO STUDIES

Antimicrobial and antioxidant activities

Mazzanti et al. (1998) published a paper in which they reported that essential oil of both *H. officinalis* L. and *H. officinalis* L. *var decumbens* possessed strong antimicrobial activity *in vitro*. The findings of the study showed that all yeasts including seven strains of *Candida albicans, Candida krusei* and *Candida tropicalis* were strongly inhibited by both species. In liquid medium the minimal inhibitory concentration (MIC) of *H. officinalis* L. was 41.2% v/v for bacteria and between 0.6 and 1.2% v/v for yeasts, while the MIC of *var. decumbens* was between 0.15 and 0.6% v/v for the Gram positive bacteria, 0.3 and 1.2% v/v for the Gram negative bacteria and 0.15 and 0.3% v/v for the yeasts. Regarding the contribution of pure components to the antimicrobial activity of the oils, pinocamphone and isopinocamphone were present in *H. officinalis* L. (4.4 and 43.3%, respectively), and instead linalol (51.7%), 1,8-cineole (12.3%) and limonene (5.1%) were predominant in *var. decumbens* representing the special microbiological properties of the essential oils. On the whole, the effect of *var. decumbens* was generally bactericidal. Linalol and 1,8-cineole, may contribute to the greater antimicrobial activity of *var. decumbens* compared to *H. officinalis* L., while limonene may be responsible for the antimycotic action observed in both oils (Mazzanti et al., 1998).

Marino et al. (2001) evaluated three groups of essential oils including hyssop oil for their inhibitory effects against nine strains of Gram negative bacteria and six strains of Gram positive bacteria. On the contrary to the previously published paper by Mazzanti et al. (1998) the findings of the study exhibited that the hyssop oil in general was less inhibitory against different strains of bacteria, suggesting variation in the composition of the essential oils according to the environmental conditions and plant chemotypes (Marino et al., 2001).

Recently, Kizil et al. (2010) evaluated antimicrobial and antioxidant activities of the essential oil of *H. officinalis (L.)* collected from wild in the Southeast Anatolian, Turkey. Isopinocamphone (57.27%), (-)-β-pinene (7.23%), (-)-terpinen-4-ol (7.13%), pinocarvone (6.49%), carvacrol (3.02%), p-cymene (2.81%) and myrtenal (2.32%) were determined as the major components of the hydrodistilled essential oil by GC-MS analysis. The essential oil with 5 and 10 µl concentrations was carried out for anti-microbial disc diffusion tests. The results of the study were indicative of the oils strong antimicrobial activities against *Staphylococcus pyogenes*, *Staphylococcus aureus, C. albicans* and *Escherichia coli*, but not against *Pseudomonas aeruginosa.* The antioxidant activity of *H. officinalis* essential oil was lower as compared to butylated hydroxytoluene and ascorbic acid. Generally, hyssop essential oil showed relatively low antioxidant activity and good antimicrobial activity against some test organisms (Kizil et al., 2010). In addition to the all cited papers indicating the importance of this genus for its antibacterial activity, publication of a patented product identified as KR 2005073080 of 2005-07-13 is an extra confirmation of the fact. The invention comprises of an anti-acne composition which exhibits excellent anti-bacterial activity to *propionbacterium acnes* as causative bacteria of acne, while no adverse reaction to human body by comprising essential oil extracted from plants including *H. officinalis* as effective ingredient. Besides, another patent product has also been reported as JP 2004262861 of 2004-09-24 with the aim of cosmetics skin-conditioning and antiwrinkle topical formulations containing 0.01% *H. officinalis* and 50% ethanolic extract (Handa, 2004; In Hong et al., 2005).

The essential oil of *H. officinalis* L. *subsp. angustifolius* and methanolic extract of the plant were examined for

their *in vitro* antimicrobial and antioxidant activities. Although, the methanol extract in the DPPH assay provided 50% inhibition at a concentration of 117.0 µg/ml and 40% inhibition at the concentration of 2 g/L in linoleic acid test system, it showed no effective activities in the antimicrobial assays, whereas, the essential oil exhibited activity against eight bacteria, ten fungi and yeast, *C. albicans*, with MIC values ranging from 15.625 to 250 µl/ml; no distinctive anti oxidant properties were achieved for the essential oil (Ozer et al., 2006).

Ebrahimzadeh et al. (2010) employed six different *in vitro* methods for evaluating antioxidant and free radical scavenging activities of methanolic extract of the aerial parts of *H. officinalis* L. *var. angustifolius* along with three other plants. They showed that it showed potent to modrate antioxidant activities in reducing powers and DPPH radical-scavenging as well as Fe2+ chelating ability assays, respectively. Although, in the case of nitric oxide and hydrogen peroxide scavenging and ferric thiocyanate methods, the results for the anti oxidant activities of *H. officinalis* L. extracts were very low and weak (Ebrahimzadeh et al., 2010). SFE extraction of antioxidant fractions from certain Lamiaceae herbs with their antioxidant capacity was evaluated (Babovic et al., 2010). Antioxidant activity of the obtained extracts, including *H. officinalis* were determined by measuring their ability to scavenge stable DPPH free radical and reactive hydroxyl radical during the Fenton reaction trapped by 5,5-dimethyl-1-pyroline-N-oxide, using electron spin resonance spectroscopy. According to the results of the study, hyssop extract showed much weaker antioxidant activity as compared to the rosemary, sage, and thyme extracts in different methods of antioxidant evaluations (Dragland et al., 2003; Fernandez-Lopez et al., 2003; Babovic et al., 2010). Ludmila and Viera (2005) assessed the antiradical activity and the reduction power of *H. officinalis* extracts in another study. All the extracts showed high activities by both evaluation criteria. Besides, among the phenolic acids, gallic acid was found to be the most active component in scavenging free radicals and caffeic acid had the highest reducing power.

In a study conducted by Glamoålija et al. (2005), essential oil of the *H. officinalis* L. was evaluated for its antifungal activity against *Mycogone perniciosa* (Mang), one of the major pathogenic diseases of the cultivated mushroom *Agaricus bisporus* (Lange) Imbach in Serbia. The findings of the study revealed its positional antifungal activity with minimal inhibitory quantity of 5 µl/ml and a minimal fungicidal quantity of 15 to 20 µl/ml. These kinds of studies have been placed in the focus of medical and aromatic plants investigations for their antifungal properties since relative biological control systems are not much used in mushroom cultivation (Ghfir et al., 1994; Ghfir et al., 1997; Glamoålija et al., 2005; Raila et al., 2009). Twelve essential oils from Mediterranean aromatic plants were tested at different doses against four fungi: *Botrytis cinerea, Penicillium italicum, Phytophthora citrophthora,* and *Rhizopus stolonifer*. The findings of the study revealed weak to moderate fungicide activities in the case of hyssop oil; however, these essential oils together with hyssop oil could be considered as natural preservatives for food products (Camele et al., 2010). Motiejunaite and Kalediene (2003) carried out an antifungal screening for essential oils of some Lamiacae plants using agar-diffusion method. In most cases including *H. officinalis* L. a complete inhibition of *Aspergillus niger* growth was observed at 0.5 to 1.5% v/v concentrations.

Pavela (2004) investigated insecticidal activities of eight medicinal plants including *H. officinalis* in third instar larvae of Egyptian cottonworm (*Spodoptera littoralis*). Methanolic extract of *H. officinalis* at the concentration of 10 % (w/v) significantly affected the growth indexes which showed a certain degree of larval toxicity with 1.78 LC_{50} and a range of 1.66 and 1.82 confidence interval of 95% (Pavela, 2004).

Anti viral activity

Crude extracts of the dried leaves of *H. officinalis* were also tested for its effectiveness on inhibition of human immunodeficiency virus (HIV) replication. Not only a safe non-toxic activity was determined for the uninfected Molt-3 cells, but also, a strong anti-HIV activity was revealed as measured by inhibition of syncytia formation, HIV reverse transcriptase (RT) and p17 and p24 antigen expression. In the experiment, either extracts from direct extraction, after removal of tannins or from the residue after dialysis of the crude extract, also showed good antiviral activity. Eventually, Kreis et al. (1990) concluded that the hyssop extracts contained caffeic acid, unidentified tannins, and possibly a third class of unidentified higher molecular weight compounds which exhibited strong anti-HIV activity, and might be useful in the treatment of patients with AIDS (Kreis et al., 1990). In another study conducted by Gollapudi et al. (1995), an isolated polysaccharide (MAR-10) from the aqueous extract of *H. officinalis* was examined for its activity against HIV-1 (SF strain) in HUT78 T cell line and primary cultures of peripheral blood mononuclear cells. They demonstrated that the MAR-10 inhibited HIV-1 replication in a concentration-dependent manner with no substantial direct toxicity or effect on lymphocyte functions or CD4+ and CD8+ T cell counts (Gollapudi et al., 1995).

Other activities

Methanolic and hexane extracts of twelve plants including *H. officinalis* that are used in traditional European medicine to treat different central nervous system disorders were tested for the symptomatic treatment of

Alzheimer's disease using Ellman's colorimetric method. Since the therapy of early and moderate stages of Alzheimer's disease is mainly based on the choline esterase inhibitors; effects of the plant extracts on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors were investigated (Wszelaki et al., 2010). Ultimately, *H. officinalis* revealed no significant inhibitory activity, as the methanolic and hexane extracts showed 5.2 ± 8.2 and 29.6 ± 2.3 AChE inhibition (%) and 11.5 ± 0.5 and 23.2 ± 2.0 BuChE inhibitions (%) at the concentrations of 100 mg/ml^{-1}, respectively (Wszelaki et al., 2010).

Animal model studies

Matsuura et al. (2004) evaluated aqueous methanol extracts of dried *H. officinalis* leaves for their α-glucosidase inhibitory activity. The active principles against α-glucosidase, prepared from rat small intestine acetone powders, were isolated and the amount of glucose derived from sucrose in the reaction mixture was measured. The extract showed inhibitory activity which led to the further isolation and identification of the responsible compounds for the α-glucosidase inhibitory activity. The structures of the two isolated compounds were determined to be (7S,8S)-syringoylglycerol-9-O-(60-O-cinnamoyl)-β-d-glucopyranoside (1) and (7S,8S)-syringoylglycerol 9-O-β-d-glucopyranoside (2) by analysis of physical and spectroscopic data together with chemical syntheses that exhibited 53 and 54% inhibitory activity at the concentration of 3×10^{-3} M for the compounds 1 and 2, respectively (Matsuura et al., 2004). In another study, Miyazaki et al. (2003) evaluated the α-glucosidase inhibitory effects of the hyssop extracts on hyperglycemia, intestinal carbohydrate absorption by examining the inhibitory effects on intestinal carbohydrate absorption in rat everted gut sac and carbohydrate-loaded hyperglycemia in mice. According to the results, in the presence of 0.5 and 1.0 mg/ml hyssop extracts, the carbohydrate-loaded excessive increase in blood glucose was inhibited within 120 min, suggesting that hyssop might be a useful supplemental food for inhibiting of postprandial hyperglycemia (Miyazaki et al., 2003). Confirming this idea, they had provided a patented product identified as JP 2004256467 of 2003-50400 from the derivatives of this plant as α-glucosidase inhibitors (Miyazaki et al., 2004). Elsewhere, the inhibitory activities of some plants used in Lebanon traditional medicine containing *H. officinalis* extracts against angiotensin converting enzyme (ACE) and digestive enzymes related to diabetes were investigated (Loizzo et al., 2008). They demonstrated that the *H. officinalis* chloroform extract was active only on the α-glucosidase enzyme, with IC50 values ranging from 127.3 to 908.4 µg/ml. At the same time the n-hexane extract of the *H. officinalis* exhibited a strong inhibitory potency against ACE (IC50 values of 52.0 µg/ml) (Loizzo et al., 2008). Churl et al. (2005) carried out an experiment to study the simulative or sedative effects of some inhaling essential oils by using a forced swimming test with mice. Inhalation of the hyssop oil ($P < 0.01$) increased the immobile state in mice that were artificially over agitated by an intra parental injection of caffeine (a psycho-stimulant). Accordingly, the authors stated that the inhaling fragrant hyssop oil possessed sedative effects (Churl et al., 2005).

Essential oils extracted from different plants including *H. officinalis* were tested for their antiplatelet activity and inhibition of clot retraction in guinea pig and rat plasma. As Tognolini et al. (2006) mentioned in their study, phenylpropanoid moiety is a favorable chemical feature for the inhibition of platelet aggregation and lack of this moiety in the hyssop oil is responsible for the oil to be inactive.

The myorelaxant effect of the hyssop essential oil on isolated preparations of guinea-pig and rabbit intestinal musculature was determined (Lu et al., 2002). Isopinocamphone, the major component of the essential oil, was considered to be responsible of the relaxing effect. Accordingly, essential oil and isopinocamphone inhibited the acetylcholine- and $BaCl_2$-induced contractions in guinea-pig ileum in a concentration-dependent manner (IC50 42.4 and 61.9 µg/ml to acetylcholine; 48.3 and 70.4 µg/ml to $BaCl_2$), whereas limonene or β-pinene left tissue contraction was unchanged. Nonetheless, synergic actions among the other several components of the essential oil could not be excluded. They believed that the myorelaxant activity induced by the hyssop oil could originate from its interaction with the plasma membrane and subsequent alteration of the ionic channels. Considering the inactivity of the β-pinene and limonene, it had been suggested that the interaction not only depends on the lipophilicity of the essential oil and its components, but also on the chemical structure of the components of the essential oil (Lu et al., 2002). Mazzanti et al. (1998) reported the spasmolytic activity of the essential oil from *H. officinalis* L. *var. decumbens*. The essential oil and its major pure components, linalool, 1,8-cineole and limonene inhibited the acetylcholine- and $BaCl_2$-induced contractions on isolated guinea-pig ileum with IC_{50} values of 37, 60, 10 and 51 µg/ml, correspondingly. Generally, it has been suggested that the hyssop oil would provide us with valuable feature of myorelaxant activity in antispasmodic remedies (Mazzanti et al., 1998).

Cytotoxicity of the essential oils of *H. officinalis* L. (HO) and *H. officinalis* var. *decumbens* (HOD) was evaluated using the brine shrimp *(Artemia salina* Leach) test. The percent of nauphii dead within 24 h was reported to determine the cytotoxic activity of the essential oils. Accordingly, HOD with LC_{50} of 156.03 µg/ml lower than HO 191.06 mg/ml revealed stronger cytotoxic activity probably in support of linalool rich in HOD (Renzini et al., 1999).

CONCLUSION

Concisely, these issues furnish the background for the experiments on the associated basic studies for the *H. officinalis* (L.) which is an important source of bioactive substances of medicinal interest. Nevertheless, several experimental studies are required to confirm the therapeutic potential of this plant and determine whether biological differences reflect the different isolation procedures, different types of plant material used, collection time, locations or different chemotypes.

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