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Phytochemistry and pharmacological profile of traditionally used medicinal plant Hyssop (*Hyssopus officinalis* L.)

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ABSTRACT

Several research publications are published on the medicinal plant *Hyssopus officinalis* L. But, the researchers find quite a difficulty to study all the publications in a short while. The present review was designed to compile and summarize all the published works on the medicinal plant *H. officinalis* L. traditionally used in several systems of medicine (1885-2018). It showed that the medicinal plant *H. officinalis* L. belonging to family Lamiaceae, is a very important culinary, medicinal and perennial plant wildly cultivated in Asia, Europe and America. It possesses numerous phytoconstituents including quercetin-7-O-β-D-apiofuranosyl-(1→2)-β-D-xylopyranoside and quercetin-7-O-β-D-apiofuranosyl-(1→2)-β-D-xylopyranoside-3'-O-β-D-glucopyranoside and possesses antioxidant, anticonvulsant, antifungal, antimicrobial, antihemolytic, antiulcer, antispasmodic and several other pharmacological activities. Its essential oil is widely being used in cosmetic, food and pharmaceutical industries worldwide. Its oil is used as an herbal medicine and very precious food additive. It is one main ingredient of the official formulation of Chartreuse. Za'atar is its well-known herbal formulation. It is a quite significant medicinal plant which can be utilized for the treatment of several diseases such as microbial infection, epilepsy, ulcer, and spasm.

INTRODUCTION

The medicinal plant *Hyssopus officinalis* L., commonly known as Hyssop (in English), Jufa (in Sanskrit), Zufah-yabis (in Hindi), Zufah (in Urdu) and belonging to family Lamiaceae, is a very important culinary, medicinal and perennial plant wildly cultivated in Asia, Europe and temperate regions of America (Fathiazad *et al.*, 2011). It is largely distributed in Central Asia to East Mediterranean. Generally, the health benefits and therapeutic uses of *H. Officinalis* are generally based on tradition rather than on any scientific validation, thus, making it an excellent candidate to assemble data, including phytochemical contents, traditional uses and biological activities accessible in recent scientific studies (Fathiazad *et al.*, 2011). Recently the biocidal (nematicidal, ixodicidal, phytotoxic and insecticidal) effects of industrial steam distilled essential oil from *H. officinalis* shown that it was effective and robustly active against *S. littoralis* (Ortiz de Elguea-Culebras *et al.*, 2018). *H. officinalis* essential oil also showed it as eco-friendly, effective and cheap mosquito larvicidal agent (Benelli *et al.*, 2017). *H. officinalis* L. affects numerous cytokines in mice with induced asthma including interleukin4 (IL-4), IL6 and IL17 and interferonγ. *H. officinalis* is an oil-rich plant which is native to the Caucasus, Turkish North Eastern Black Sea region, North Western Iran and Southern Anatolia which is an extremely esteemed medicinal plant (Kizil *et al.*, 2008).

Hyssopus officinalis stimulates digestion and acts as antiseptic. The plant was in a vegetative phase in the month of mid-June, the start of flowering in mid-July, full blooming in mid of August and after flowering in mid of September. The effect of plant harvesting and plant spacing (30 × 30, 40 × 40, 50 × 50 cm) upon the quantity and yield of *H. officinalis* herb was evaluated in the year from 2006 to 2008. Considerably, larger plant yield was found from the plant after flowering, just like the dry yield of the plant without stems. It was also revealed during this study that the highest fresh plant yield of 1.47 kg/m^2 was from plant grown in 40 × 40 cm spacing, similarly to the dry yield of the plant without stems. The contents of oil, dry matter, chlorophyll, *l*-ascorbic acid, flavonoids, carotenoids, and tannins were not significantly

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affected by the plant spacing. However, the contents of *l*-ascorbic acid, essential oil, chlorophyll and carotenoids in *H. officinalis* herb were significantly affected by the harvest term (Zawislak, 2011).

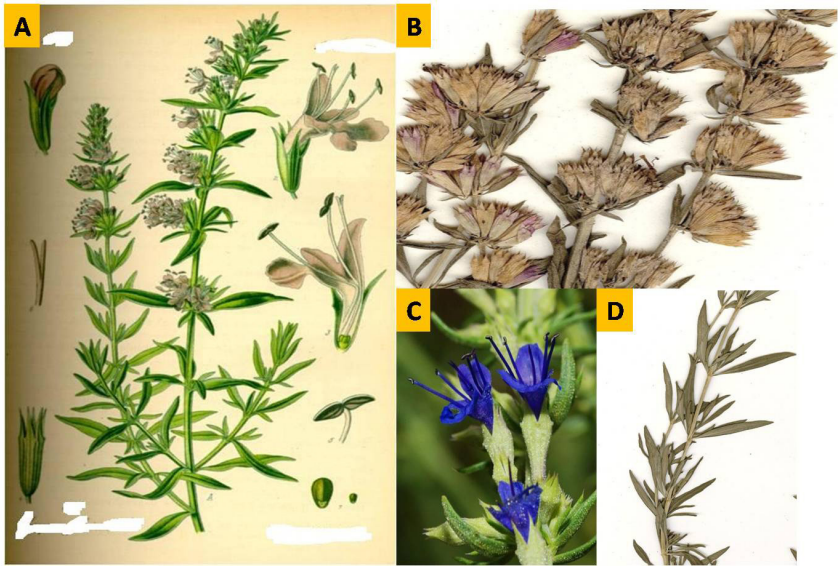

Fig. 1: Images of the plant *Hyssopus officinalis* L. and its parts: [A]. A twig from the whole plant of *H. officinalis*, **[B].** Fruits, **[C].** Flowers, and **[D].** Leaves (Thome, 1885).

The moderate temperature for proper germination of *H. officinalis* was established to be at 20°C-30°C. The maximum germination rate was obtained at 30°C. So, the warmer temperature is very suitable for it. The optimum seedlings growth was established to be at 30°C (Mijani *et al.*, 2013). Application of biofertilizers *Pseudomonas fluorescens/Bacillus subtilis/ Azospirillum* (Super Nitro Plus); *Azotobacter/Azospirillum* (Nitroxin), *Glomus intraradices* (*Mycorrhizal inoculant*) and *Pseudomonas fluorescens* enhanced the yield and other plant criteria of *H. officinalis*. *H. officinalis* had shown better plant criteria with the proper application of a mixture of *Glomus intraradices* and *Pseudomonas fluorescens*; and Super Nitro Plus (Tabrizi *et al.*, 2008). Images of the plant *Hyssopus officinalis* L. and its parts are shown in Figure 1.

TRADITIONAL USES

The plant *H. officinalis* has been used traditionally for medicinal purposes (Fathiazad *et al.*, 2011). Its essential oil is widely being used in cosmetic, food and pharmaceutical industries worldwide. In herbal systems of medicine, *H. officinalis* is supposed to possess soothing, expectorant, and cough suppressant properties. It can stimulate the gastrointestinal system. It is being used in formulations of sauce and also as an ingredient of food in flavor industry (Kazazi *et al.*, 2007). Its oil is used as an herbal medicine and very precious food additive. It is moderately used for food preparation. Fresh herb of *H. officinalis* is usually used in cooking (Fernández-López *et al.*, 2003). Za'atar is a well-known herbal mix of Middle East where dried leaves of *H. officinalis* is used as the main ingredient. The essence of *H. officinalis* is used in food preparation to a minor extent. *H. officinalis* is used to flavor liqueur and is one main ingredient of the official formulation of Chartreuse (Kazazi *et al.*, 2007). It is generally used by beekeepers to produce an aromatic and rich honey. Its leaves are used as an aromatic condiment and have a slightly bitter taste due to its tannins and an intense minty aroma (Paun *et al.*, 2014).

PHYTOCHEMISTRY

Total flavonoids and phenolic contents found to be highest in *H. officinalis* L. ssp. *angustifolius* leaves aqueous extracts were 1.3% (gallic acid equivalent) and 4.7% respectively (Hatipoglua *et al.*, 2013). Proanthocyanidine was present in a very high concentration in aqueous, chloroform and hexane extracts of the leaves, predominantly in chloroform extract of the leaves (10250 mg/L) (Hatipoglua *et al.*, 2013). HPLC analysis validated the occurrence of antioxidant phenolics such as caffeic acid (111.09 g/g) and chlorogenic acid (166.21 g/g) in methanolic extract of the leaves (Hatipoglua *et al.*, 2013).

Total phenol content in the *n*-butanol and ethylacetate extracts of the aerial parts was found to be 246 mg gallic acid equivalent (GAE)/g and 51 mg GAE/g. The major flavonoid apigenin-7-O-*β*-D-glucuronide was isolated from the hydromethanolic extract of aerial parts. The other main compounds isolated were myrtenyl acetate, camphor, germacrene and spathulenol (Fathiazad *et al.*, 2011).

Main constituents in *H. officinalis* extract from root removed whole plant in various supercritical fluid conditions of extraction were sabinene (4.2%-17.1% w/w), iso-pinocamphene (0.9%-16.5%) and pinocamphene (0.7%-13.6%) (Kazazi *et al.*, 2007).

The main constituents in *H. officinalis* were some polyphenolic compounds principally including flavonoids luteolin, diosmin, quercetin, apigenin and their glucosides along with some phenolic acids such as caffeic acids p-hydroxybenzoic, syringic, ferulic, protocatechuic and chlorogenic acid. Essential oils from *H. officinalis* aerial parts had shown some principal constituents such as terpenoids ***β***-pinene, isopinocamphone and pinocamphone (Fathiazad *et al.*, 2011).

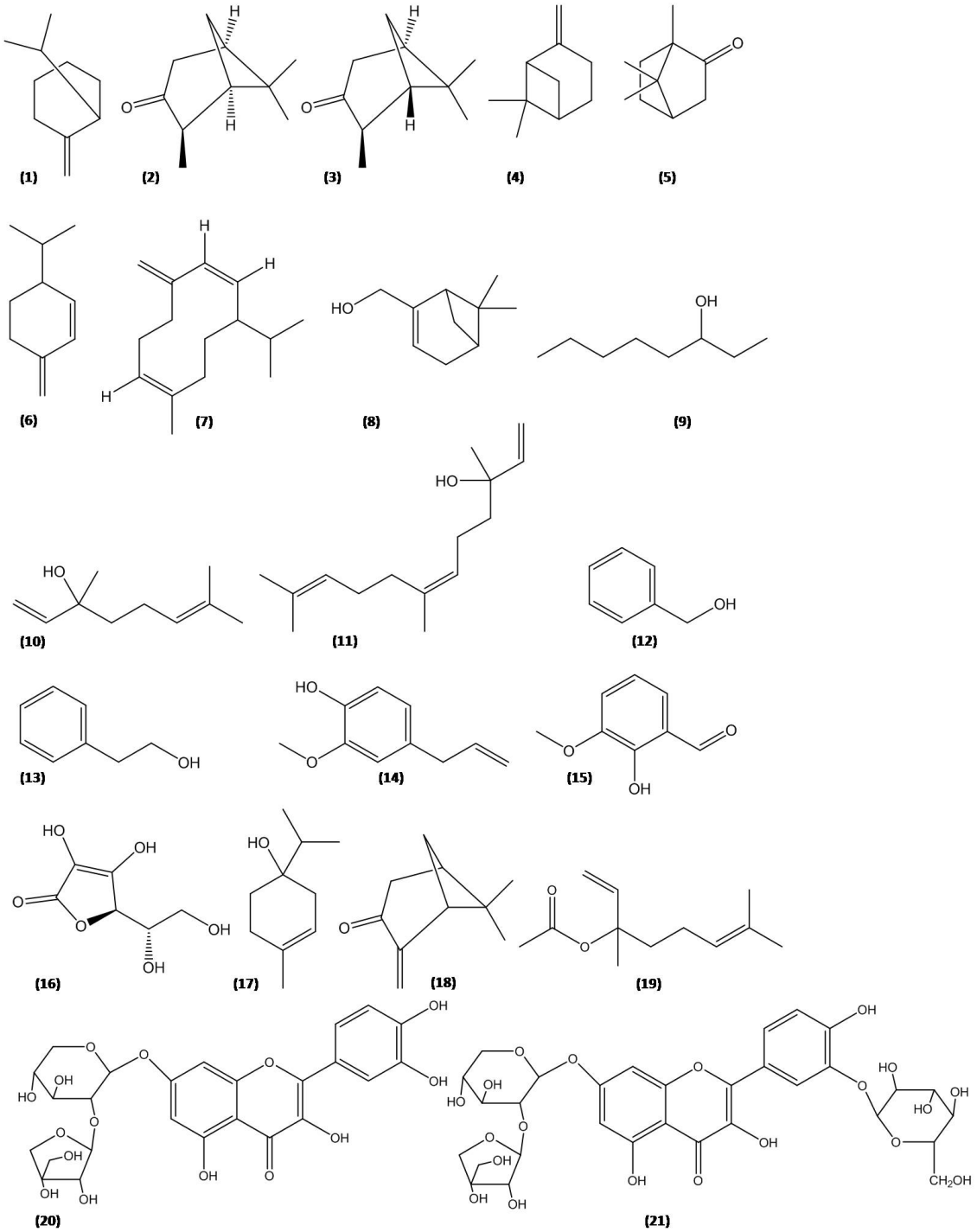

Fig. 2: Phytoconstituents reported in *H. officinalis*: Sabinene (**1**), iso-pinocamphene (**2**), pinocamphene (**3**), *β*-pinene (**4**), Camphor (**5**), *α*,*β*-phellandrene (**6**), germacrene D (**7**), Myrtenol (**8**), octan-3-ol (**9**), Linalool (**10**), *cis*-nerolidol (**11**), benzyl alcohol (**12**), Phenylethanol (**13**), Eugenol (**14**), *o*-vanillin (**15**), *l*-ascorbic acid (**16**), terpinen-4-ol (**17**), Pinocarvone (**18**), Linalyl acetate (**19**), quercetin-7-O-*β*-D-apiofuranosyl-(1→2)-*β*-D-xylopyranoside (**20**), quercetin 7-O-*β*-D-apiofuranosyl-(1→2)-*β*-D-xylopyranoside-3'-O-*β*-D-glucopyranoside (**21**).

Yields of essential oil hydrodistilled from above ground portions of *H. officinalis* raised via seeds were 1.18% on dry herbage weight basis and 0.25% on fresh herbage weight basis. The essential oil (95.6%) had shown the presence of six sesquiterpene hydrocarbons (0.35%), one phenol (0.2%), five oxygenated monoterpenes (60.5%) and seven monoterpene hydrocarbons (32.3%) in gas chromatographic and mass spectrometry (GCMS) analysis. The major constituents of the camphor odor oil were pinocamphone (49.1%), *β*-pinene (18.4%), isopinocamphone (9.7%) (Garg *et al.*, 1999).

The *β*-pinene, camphor, pinocamphone plus 15 other terpenes were present in essential oils at three stages of development in GCMS analysis, among which were myrtenol derivatives, germacrene D, *α*-phellandrene and *β*-phellandrene

and isopinocamphone. It showed the occurrence of glycosidically bound volatiles also in low concentration (0.01%-0.06%) such as bicyclic terpenes verbenol and myrtenol in leaves (Schulz and Stahl-Biskup, 1991).

Aqueous methanolic extract of leaves of dried *H. officinalis* showed an α-glucosidase inhibitory activity and also showed (7S,8S)-syringoylglycerol-9-O-(6'-O-cinnamoyl)-β-D-glucopyranoside and (7S,8S)-syringoylglycerol-9-O-β-D-glucopyranoside as evident from spectroscopic data of isolated compounds (Matsuura *et al.*, 2004).

The essential oil steam distilled from *H. officinalis* showed β-pinene (16%) and 1,8-cineole (53%) as the major constituents in GCMS analysis (Ortiz de Elguea-Culebras *et al.*, 2018).

The essential oil from the herb of *H. officinalis* showed 31 compounds in steam distilled oil, 36 compounds in hydrodistilled oil and 27 compounds in hydrodistilled oil by Dean-Stark apparatus in GCMS analysis. All the analyzed oil samples showed the presence of isopinocamphone as the main constituent (40.07%–45.45%) (Wesolowska *et al.*, 2010).

The primary active compounds in oil of *H. officinalis* were *cis*-3-pinanones and *trans*-3-pinanones (Hold *et al.*, 2002).

The *H. officinalis* essential oil showed saturated bicyclic monoterpene ketones isopinocamphone and pinocamphone with few myrtenol derivatives (Karp and Croteau, 1992).

There is a high capability to save water through longer irrigation intervals of *H. officinalis* (e.g. 14 days) in Khorasan's semi-arid conditions as the crop serves as an alternative income source in the years of dry conditions (Khazaiea *et al.*, 2008).

Stage of blooming and environmental conditions seriously affect the oil contents in *H. officinalis* with the highest oil contents and yield at the post-blooming stage. Isopinocamphone was found to the primary component (47.9%-51.4%) amongst the twenty-nine components in the analyzed *H. officinalis* essential oil analyzed by GCMS analysis (Kizil *et al.*, 2008).

The major compounds shown in essential oil from supercritical extracts of *H. officinalis* were terpinen-4-ol (5%), 1,8-cineol (75%), β-pinocarvone (4%) and pinene (4%) along with some heavier compounds (Langa *et al.*, 2009).

Dimethyl sulfoxide (DMSO) extracts of *H. officinalis* leaves showed two main phenolics in high-performance liquid chromatography (HPLC) analysis along with diosmin and isoferulyl-D-glucose ester as the major constituents (Mario *et al.*, 1998).

The essential oil of Spanish *H. officinalis* showed elevated contents of β-pinene (16.82%) and 1,8-cineole (52.89%) as the main constituents in gas chromatography (GC) analysis (Vallejo *et al.*, 1995).

The volatile components in four *H. officinalis* phenotypes differentiated by the color of their corolla showed three ketones pinocarvone, isopinocamphone and pinocamphone as the chief components which can be used to differentiate these phenotypes. The phenotype with the blue flower was more intense in odor than the other phenotypes (Kerrola *et al.*, 1994).

The new flavonoid glycosides namely quercetin-7-O-β-D-apiofuranosyl-(1→2)-β-D-xylopyranoside-3'-O-β-D-glucopyranoside and quercetin-7-O-β-D-apiofuranosyl-(1→2)-β-D-xylopyranoside were isolated from the whole herbs of H. officinalis cultivated in Xinjiang Uygur Autonomous Region of China (Wang and Yang, 2010).

Isopinocamphone and pinocamphone (43.3% and 4.4% respectively) were present in *H. officinalis* according to the ISO 9841 Standard (1991 E) but they were lacking in var. *decumbens* where limonene (5.1%), 1,8-cineole (12.3%) and linalol (51.7%) instead were predominantly present (Mazzanti *et al.*, 1998a).

GCMS analysis showed that β-pinene (10.8% and 10.5%), isopinocamphone (29% and 3.2%) and pinocamphone (18.5% and 34%) were the major constituents in the two essential oils of plant *H. officinalis* which were grown in different areas near Urbino (Italy, Marche) (Fraternale *et al.*, 2004).

GCMS analysis showed that the myrtenal (2.32%), *p*-cymene (2.81%), carvacrol (3.02%), pinocarvone (6.49%), (−)-terpinen-4-ol (7.13%), (−)-β-pinene (7.23%) and isopinocamphone (57.27%) were present as the major constituents in the hydrodistilled essential oil of *H. officinalis* leaves which were collected in the Turkey Southeast Anatolian from wild (Kizil *et al.*, 2010).

High-performance liquid chromatography and mass spectrometry (HPLC-MS) analysis showed free flavonoid aglycons (quercetin, luteolin), flavonoid glycosides (quercitrin, isoquercitrin and rutin) and phenolic acid derivatives (ferulic, chlorogenic, *p*-coumaric, caffeic, gentisic and caftaric acids) in dissimilar concentrations in *H. officinalis* ethanolic extract along with large amount (77.72 mg/g) of the polyphenolic compounds (Vlase *et al.*, 2014).

The yield of hydrodistilled essential oil in stem, flower, and leaf of *H. officinalis* collected from Western-Himalaya (Chamoli, Uttarakhand, India) varied from 0.22% to 4.4%. Fifty-seven constituents (88.4%) of the stem oil, 44 constituents (99.4%) of the flower oil and 57 constituents (99.8%) of the leaf oil were identified in it. Major components of the oils were *trans*-pinocamphone (<0.05%–1.3%), myrcene (0.5%–1.3%), myrtenol (1.4%–1.7%), isopimara-9(11),15-diene (<0.05%–1.9%), sabinene (0.8%–1.9%), β-phellandrene (1.8%–3.2%), myrtenyl methyl ether (2.7%–3.0%), 1,8-cineole (2.9%–8.0%), β-pinene (5.7%–9.3%), pinocarvone (5.5%–24.9%) and *cis*-pinocamphone (49.7%–57.7%). The leaf and stem oil were relatively similar in terms of pinocarvone and *cis*-pinocamphone content. The flower oil was differentiable from the leaf and stem oils due to the presence of a higher quantity of pinocarvone (Pandey *et al.*, 2014).

Steam distilled oil from fresh aerial parts of three Italian *H. officinalis* strains wildly grown in diverse natural habitats of the Abruzzi region (Central Italy) shown thirty-three compounds in it. One of the strains shown very high content of limonene (15.9%) and methyl eugenol (43.9%), another contained 1,8-cineole (23.1%) and β-pinene (24.7%) as main components, while the third one was with high contents of β-pinene (19.3%) and myrtenol (32.6%) (Piccaglia *et al.*, 1999).

H. officinalis essential oil content was ranged from 0.13% to 0.26% and the content improved with time. The yield of *H. officinalis* essential oil ranged from 7.3 kg/ha to 19.6 kg/ha. The major components were β-pinene (5%–15%) and isopinocamphene plus pinocamphene (57%–75%). Delayed harvest improved myrcene, β-pinene, and limonene plus cineole concentrations but reduced isopinocamphone plus pinocamphone. The chemical composition of *H. officinalis* oil from Mississippi

was same as commercial oils from US, France, Canada and Bulgaria (Zheljazkov *et al.*, 2012).

The essential oils from *H. ofticinalis* L. ssp. *aristatus* (Godr.) Briq. Wild at two stages of development were same in composition with 1,8-cineole (48.2% and 39.6%), isopinocarnphone (16.3% and 29.2%) and *β*-pinene (11.4% and 39.6%) as major components. However, the commercial essential oil from *H. officinalis* contains larger amounts of *β*-pinene (14.2%), pinocamphone (10.3%) and isopinocamphone (40.2%) (Tsankova *et al.*, 1993). The main phytoconstituents reported in *H. officinalis* L. are shown in Figure 2.

PHARMACOLOGICAL ACTIVITIES

Antioxidant activity

Two novel flavonoid glycosides quercetin-7-O-*β*-D-apiofuranosyl-(1→2)-*β*-D-xylopyranoside and quercetin-7-O-*β*-D-apiofuranosyl-(1→2)-*β*-D-xylopyranoside-3'-O-*β*-D-glucopyranoside isolated from *H. officinalis* performed the potent scavenging of stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) (Wang and Yang, 2010).

H. officinalis var. *angustifolius* stems, leaves, and flowers ethanolic extracts showed moderate iron (II) chelating ability, good scavenging hydrogen peroxide, good antioxidant activity in the hemoglobin-induced linoleic acid model and good antioxidant activity in a concentration-dependent manner. Inhibitory concentration fifty percent (IC_{50}) for DPPH scavenging were found to be 148.8 ± 4.31 µg/ml for flowers, 208.2 ± 6.45 µg/ml for leaves and 79.9 ± 2.63 µg/ml for stems (Alinezhad *et al.*, 2013).

H. officinalis extract blended in pork meat samples was seen to inhibit degradation of heme pigments and lipid oxidation caused by cooking and storage for 8 days at 4°C. It also stabilized the red meat color and delayed metmyoglobin formation during cooked meat storage (Fernández-López *et al.*, 2003).

Aqueous extract showed better DPPH radical scavenging activity as compared to chloroform and hexane automated extracts of *H. officinalis* var *angustifolius* leaves and water distilled Clevenger derived essential oil. The IC_{50} values of the chloroform extract, water extract and methanol-water (1:1) macerated extract were 28.80, 18.80 and 250 µg/ml, respectively. The nonpolar extract was more active in *β*-carotene/linoleic acid test system (Hatipoglua *et al.*, 2013).

The antioxidant activity of *H. officinalis* essential oil from Turkey Southeast Anatolian for scavenging of DPPH radical was lower as compared to the standards butylated hydroxytoluene (BHT) and ascorbic acid (Kizil *et al.*, 2010).

H. officinalis ethanolic extract showed a good antioxidant activity as witnessed by Trolox equivalent antioxidant capacity assay, electron paramagnetic resonance radical detection assay, DPPH radical scavenging assay and hemoglobin ascorbate peroxidase activity inhibition assay (Vlase *et al.*, 2014).

The purified flavonoid (apigenin-7-*O*-*β*-D-glucuronide) from *H. officinalis* showed weak scavenging of DPPH radical (IC_{50} = 116 × 10^{-3} mg/ml). The *n*-butanol extract, because of the highest content of total phenolics (246 mg GAE/100g) had the best scavenging of DPPH radical (IC_{50} = 25 × 10^{-3} mg/ml) while ethylacetate extract, the IC_{50} value of 103 × 10^{-3} mg/ml (Fathiazad *et al.*, 2011). *H. officinalis* essential oil did not modify the ruminal fermentation. Antioxidant activity was found to be 2039 µmol Trolox equivalent per liter (TE/L) (Zheljazkov *et al.*, 2012).

Anticonvulsant activity

Trans-3-pinanones, *cis*-3-pinanones and *H. officinalis* oil acted as $GABA_A$ receptor antagonists based on inhibition of 40-ethynyl-4-*n*-[2,3-$3H_2$]propylbicycloorthobenzoate ([3H] EBOB) binding in brain membranes of mouse (IC_{50}: 35-64 mM) and well supported by mouse tonic/clonic convulsions (intraperitoneal (*i.p.*) lethal dose fifty percent (LD_{50}) 175 mg/kg to >250 mg/kg) alleviated by diazepam. 2-Hydroxy-*cis*-3-pinanone and 2,10-dehydro-3-pinanone, the *cis*-3-pinanone metabolites exhibited reduced toxicity and potency for inhibition of [3H] EBOB binding (Hold *et al.*, 2002).

Antifungal activity

H. officinalis oil (0.4%) entirely inhibited the mycelium growth of *Pyricularia oryzae* and *Pyrenophora avenae*, the plant pathogenic fungi, *in vitro* in agar medium. Pinocamphone, isopinocampheol and *l*-bornyl acetate, the components of *H. officinalis* oil, completely inhibited fungal growth individually and, also in combinations when mixture contained isopinocampheol also. *P. oryzae* mycelial growth was less affected by them. *H. officinalis* oil reduced germination of uredospores of *Uromyces viciae-fabae* and *Botrytis fabae conidia* but, its effects on pathogen infection were less clear-cut. Thus, its effects against apple powdery mildew and barley powdery mildew were variable although 0.05% *H. officinalis* oil reduced rust infection of broad bean when applied 1, 2 or 3 days before, or 1 or 2 days after inoculation (Letessier *et al.*, 2001).

The two essential oils from *H. officinalis* grown in two different localities near Urbino (Italy, Marche) and grown at 1000 m above sea level showed very high antifungal activity against different phytopathogenic fungi strains (Fraternale *et al.*, 2004).

The fractionated and isolated growing hyphal *Aspergillus fumigatus* cell walls cultured in the absence or presence of essential oil from *H. officinalis* showed that the presence of essential oil caused a decrease in levels of uronic acid, proteins and neutral sugars, whereas phosphorus, lipids, and amino sugars levels were increased. Neutral sugars were mainly consisted of galactose, mannose, and glucose, while the amino sugars consisted of galactosamine and glucosamine as observed in HPLC analysis. *H. officinalis* oil presence induced marked changes in the content of galactosamine and galactose in the culture medium. *H. officinalis* oil also induced similar changes in the different fractions with a more distinct effect on the major components (Ghfir *et al.*, 1997).

The biocidal (nematicidal, ixodicidal, phytotoxic and insecticidal) effects of industrial steam distilled essential oil from *H. officinalis* was effective and robustly active against *S. littoralis* (Ortiz de Elguea-Culebras *et al.*, 2018).

Antimicrobial activity

The disc diffusion tests carried out on Gram+ve (*Enterococcus spp*. and *Staphylococcus aureus*) and Gram−ve bacteria (*Pseudomonas spp*., *Proteus mirabilis, Escherichia coli, Klebsiella oxytoca,* and two strains of *Salmonella spp*.) showed

an antimicrobial activity insignificant for *H. officinalis* essential oil from Italy (Piedmont), but broader, and in a few cases more evident (*E. coli* and *Enterococcus spp.*) and for essential oil of var. *decumbens* (Jordan & Fourr.). All yeasts (*C. tropicalis, C. krusei* and seven strains of *Candida albicans*) were robustly inhibited by both species. In liquid medium, the MIC of *H. officinalis* was between 0.6% and 1.2% v/v for yeasts and always 41.2% v/v for bacteria, while the MIC of var. *decumbens* was between 0.15% and 0.3% v/v for the yeasts, 0.3% and 1.2% v/v for the Gram−ve bacteria and 0.15% and 0.6% v/v for the Gram+ve bacteria. *H. officinalis* var. *decumbens* was bactericidal. 1,8-Cineole and linalool contributed to the greater antimicrobial activity of var. *decumbens* in comparison with *H. officinalis*, while limonene was responsible for the antimycotic action observed in both oils (Mazzanti *et al.*, 1998a).

H. officinalis has moderate *in vitro* antimicrobial activity against Gram+ve and Gram−ve bacteria and antioxidant activity together with antifungal, antiviral and insecticidal activities. It has shown ***α***-glucosidase inhibitory, antiplatelet and myorelaxant activities *in vivo* (Fathiazad *et al.*, 2011).

The 5 µl and 10 µl of *H. officinalis* essential oil from Southeast Anatolian, Turkey exhibited significant antimicrobial activity against *Staphylococcus pyogenes, Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*, but not against *Pseudomonas aeroginosa* in disc diffusion test (Kizil *et al.*, 2010; Vlase *et al.*, 2014).

The coriander and *H. officinalis* essential oils (0.02% v/w) inhibited the growth of Enterobacteriaceae and the development of undesirable sensory changes in vacuum-packed beef meat stored at 6 ± 1°C and 0.5 ± 0.5°C for 15 days. The effect on the total viable bacterial count of lactic acid bacteria and other groups of microorganisms was minor and similar for both oils. These additives did not significantly affect protein electropherograms, meat pigments, protease activity, pH levels and amino nitrogen levels indicating the limited effect of these oils in the concentrations applied on preserving vacuum-packed minced beef (Michalczyk *et al.*, 2012).

The essential oil from *H. officinalis* L. ssp. *angustifolius* showed antimicrobial activity *in vitro* against a yeast *C. albicans*, fungi, and bacteria with minimum inhibitory concentration (MIC) of 15.62 µl/ml−250 µl/ml where the methanolic extract was inactive. The methanolic extract showed IC_{50} of 117.0 µg/ml in DPPH assay while 40% inhibition at 2 g/L concentration in a linoleic acid system where essential oil was inactive (Özer *et al.*, 2006).

Antidiabetic activity

Aqueous methanolic extract of dried *H. officinalis* leaves (300 mg/kg and 100 mg/kg body weight, b.wt.) showed an *α*-glucosidase inhibitory activity in mice (Miyazaki *et al.*, 2003; Matsuura *et al.*, 2004). It has antidiabetic activity but it is contraindicated in patients with liver affections (Akram *et al.*, 2013).

Antihemolytic activity

H. officinalis extracts showed very good antihemolytic activity against H_2O_2-induced hemolysis in rat erythrocytes (48.51 ± 2.27 µg/ml for flowers, 19.47 ± 0.73 µg/ml for leaves and IC_{50} 63.1 ± 2.65 µg/ml for stems) (Alinezhad *et al.*, 2013).

Antiulcer activity

Pre-treatment with 100 mg/kg and 125 mg/kg b. wt. of *H. officinalis* ethanolic extract to albino rats 1 h before the administration of ethanol showed a great antioxidant and antiulcer potential depicted by decreased nitric oxide level, decreased reactive oxygen species (ROS) generation, improved integrity of stomach and improved mucus secretion supporting its traditional use in folk medicine (Saini and Sharma, 2012).

The *H. officinalis* extract enriched in polyphenolic compounds (phenolic acids, tannins, and flavonoids) showed a significant inhibition (92.67%) against urease obtained from jack bean and low inhibition (19.6%) against *α*-chymotrypsin which could be considered as a possible remedy in ulcer treatment (Paun *et al.*, 2014).

Antileishmaniasis activity

Ointment-based *H. officinalis* extracts applied topically two times daily for 20 days effectively reduced the cutaneous ulcer size and burden of Leishmania parasite in the spleen as compared to glucantime in specific BALB/C mice (Akhlaghi *et al.*, 2014).

Mosquito larvicide activity

H. officinalis essential oil showed lethal concentration (LC_{50}) values higher than 90 µl/L in acute toxicity study against binary mixtures of *Culex quinquefasciatus* vector, a vector of lymphatic filariasis, supporting it as eco-friendly, effective and cheap mosquito larvicides (Benelli *et al.*, 2017).

Airway remodeling inhibition

The expression of both TIMP-1 and MMP-9 decreased after being treated with standard dexamethasone and Uygur herb *H. officinalis* accompanied by the relieved pathological changes including smooth muscle proliferation, mucus secretion and collagen deposition supporting its airway remodeling inhibition by correcting the imbalance of MMP-9/TIMP-1 ratio (Ma *et al.*, 2014a).

Antispasmodic activity

Essential oil from *H. officinalis* var. *decumbens* and linalool non-competitively inhibited the barium chloride-induced and acetylcholine-induced contractions of isolated guinea pig ileum in a concentration-dependent manner (IC_{50} values: *H. officinalis* var. *decumbens* 60 mg/ml and 37 mg/ml; linalool 51 mg/ml and 10 mg/ml). 1,8-Cineole and limonene also showed only a weak spasmogen action (Mazzanti *et al.*,1998b).

Anti-inflammatory activity

The eosinophils ratio in bronchoalveolar lavage fluid and the levels of serum immunoglobulins Ig*G* and Ig*E* in the *H. officinalis* treatment group were decreased compared to ovalbumin and dexamethasone-treated group (chronic asthmatic) observed by enzyme-linked immunosorbent assay (ELISA). *H. officinalis* also affected the immune regulation (Ma *et al.*, 2014b).

Muscle relaxant activity

The essential oil of *H. officinalis* inhibited the barium chloride ($BaCl_2$)-induced and acetyl choline (ACh)-induced

muscle contractions in the isolated guinea-pig ileum. Essential oil also decreased the basal tone and reduced the amplitude of spontaneous movements in isolated rabbit jejunum (Lu *et al.*, 2002).

Antiasthmatic activity

Uygur herb *H. officinalis* could affect the levels of some cytokines (such as IL-17, IL-6, IL-4 and interferon (IFN)-γ) in asthmatic mice (Ma *et al.*, 2014a).

Anti-HIV activity

Methanolic extracts, subsequent to ether, chloroform and chloroform-ethanol extractions of dried leaves of *Hyssopus officinalis*, showed very strong anti-HIV (Human Immunodeficiency Virus) activity as measured by inhibition of HIV reverse transcriptase, p17 and p24 antigen expression and syncytia formation probably due to caffeic acid and it may be useful in the treatment of patients with acquired immunodeficiency syndrome (AIDS) (Kreis *et al.*, 1990).

A polysaccharide from *H. officinalis* aqueous extract showed anti-HIV activity against HIV-1 in HUT78 T cell line as demonstrated by the inhibition of syncytia formation and HIV-1 p24 antigen (Gollapudi *et al.*, 1995).

A summary of different pharmacological activities of *Hyssopus officinalis* L. is shown in Table 1.

Table 1. Different pharmacological activities of *Hyssopus officinalis* L.

Pharmacological activities	References
Antioxidant activity	Fernández-López *et al.*, 2003; Wang and Yang, 2010; Kizil *et al.*, 2010; Fathiazad *et al.*, 2011; Zheljazkov *et al.*, 2012; Alinezhad *et al.*, 2013; Hatipoglua *et al.*, 2013; Vlase *et al.*, 2014
Anticonvulsant activity	Hold *et al.*, 2002
Antifungal activity	Ghfir *et al.*, 1997; Letessier *et al.*, 2001; Fraternale *et al.*, 2004; Ortiz de Elguea-Culebras *et al.*, 2018
Antimicrobial activity	Mazzanti *et al.*, 1998a; Özer *et al.*, 2006; Kizil *et al.*, 2010; Fathiazad *et al.*, 2011; Michalczyk *et al.*, 2012; Vlase *et al.*, 2014
Antidiabetic activity	Miyazaki *et al.*, 2003; Matsuura *et al.*, 2004; Akram *et al.*, 2013
Antihemolytic activity	Alinezhad *et al.*, 2013
Antiulcer activity	Saini and Sharma, 2012; Paun *et al.*, 2014
Antileishmaniasis activity	Akhlaghi *et al.*, 2014
Mosquito larvicide activity	Benelli *et al.*, 2017
Airway remodeling inhibition	Ma *et al.*, 2014a
Antispasmodic activity	Mazzanti *et al.*,1998b
Anti-inflammatory activity	Ma *et al.*, 2014b
Muscle relaxant activity	Lu *et al.*, 2002
Antiastmatic activity	Ma *et al.*, 2014b
Anti-HIV activity	Kreis *et al.*, 1990; Gollapudi *et al.*, 1995

METABOLISM OF PRINCIPAL ACTIVE INGREDIENTS IN *H. OFFICINALIS* OIL

The major metabolite of the principal active ingredients in *H. officinalis* oil i.e., *cis*-3-pinanone in each P_{450} system and in the brain of the *ip* treated mouse was 2-hydroxy-*cis*-3-pinanone, and two minor metabolites were hydroxypinanones other than 2-hydroxy-*trans*-3-pinanone and 4-*S*-hydroxy-*cis*-3-pinanone in GCMS analysis. The urine from oral *cis*-3-pinanone treatment examined on a qualitative basis contained conjugates of metabolites observed in the microsomal systems plus 2,10-dehydro-3-pinanone. *Trans*-3-pinanone was metabolized more slowly than the *cis*-isomer in each system to give hydroxy derivatives different than those derived from *cis*-3-pinanone (Hold *et al.*, 2002).

A microsomal preparation from leaf epidermis oil glands of *H. officinalis* converts the parent olefin (−)-β-pinene to the allylic alcohol. (+)-*trans*-pinocarveol that presumably gives rise to (−)-pinocamphone and (−)-isopinocamphone by subsequent oxidation and two stereochemical alternatives for reduction of the conjugated double bond. The same preparation catalyzes the hydroxylation of (−)-α-pinene to (−)-myrtenol at a slower rate. The pinene hydroxylase from the oil glands of *H. officinalis* has characteristics of a distinct cytochrome P-450 species. Parent cyclic olefins were metabolized by a pathway involving allylic oxidation and conjugate reduction (Karp and Croteau, 1992).

CONCLUSION

Present review elaborated that the medicinal plant *H. officinalis* L. possesses numerous phytoconstituents such as quercetin-7-O-β-D-apiofuranosyl-(1→2)-β-D-xylopyranoside and quercetin-7-O-β-D-apiofuranosyl-(1→2)-β-D-xylopyranoside-3'-O-β-D-glucopyranoside and also possesses various pharmacological or biological activities such as antioxidant, anticonvulsant, antifungal, antimicrobial, antihemolytic, antiulcer and antispasmodic activities. The plant *H. officinalis* L. is a quite significant medicinal plant possessing several phytoconstituents of pharmaceutical importance and which can be utilized for the amelioration and treatment of several diseases such as microbial infection, epilepsy, ulcer, and spasm. The present review compiled and summarized the significant published works on the medicinal plant *H. officinalis* L. traditionally used in several systems of medicine such as Unani and Ayurveda covering the phytochemistry, pharmacology and its traditional uses which can be further evaluated to achieve lead molecules in the search of novel herbal drugs.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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