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A review of chemical components and pharmacological effects of *Melissa officinalis* L

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ABSTRACT

Melissa officinalis is a plant growing and cultivated in some parts of Iran. The leaves of lemon balm, M. officinalis L. (Lamiaceae) are used in Iranian folk medicine for their digestive, carminative, antispasmodic, sedative, analgesic, tonic and diuretic as well as for functional gastrointestinal disorders. The aim of this study was to overview its therapeutic effects than its nutritive and industrial effects. This review article was carried out by searching studies in PubMed, Medline, Web of Science, and Iran Medex databases .The initial search strategy identified about 128 references. In this study, 113 studies was accepted for further screening and met all our inclusion criteria [in English, full text, therapeutic effects of Melissa officinalis L and dated mainly from the year 1964 to 2015.The search terms were "Melissa officinalis L.", lemon balm, "therapeutic properties","pharmacological effects". It is commonly used for its anti-herpes and anti-viral and anti-HIV, antioxidant, antimicrobial, anticancer and anti- tumor, anti-stress and anti-anxiolytic and antidepressant, anti-Alzheimer, anti-cardiovascular diseases, memory improving and concentration, anti-inflammatory effects.It was said to be good for insomnia and dyssomina. Melissa officinalis l. is widely used for therapeutic and non-therapeutic purposes that trigger its significant value. Various combinations and numerous medicinal properties of its extract, oil, and leaves demand further and more studies about the other useful and unknown properties of this multipurpose plant.

Keywords: *Melissa officinalis* L., Phytochemicals, Therapeutic effects, Pharmacognosy, Alternative and complementary medicine.

INTRODUCTION

Melissa officinalis L. also known as lemon balm, bee balm, honey balm[1], is a perennial herb[2] belonging to Lamiaceae family[3, 4].it is native to southern Europe and northern Africa, Caucasus and northern Iran [5], the Eastern Mediterranean region and Western Asia, as well as tropical countries [Brazil][6]. In Iran, this plant is known locally by the names Badranjbooye, Varangboo and Faranjmoshk[7].

Historically lemon balm has been said to possess sedative/tranquilizing, anti-gas, fever-reducing, antibacterial, spasmolytic, hypotensive, memory-enhancing, menstrual-inducing, and thyroid-related effects [8-10],spasmolytic,

nervous sedative[11], its oil has been reported as having antibacterial, antifungal, antiparasitic and antispasmolytic activities[12, 13]. It was used in the Iranian traditional system of medicine for the treatment of headaches, flatulence, indigestion, colic, nausea, nervousness, anemia, vertigo, syncope, malaise, asthma, bronchitis, amenorrhea, cardiac failure, arrhythmias, insomnia, epilepsy, depression, psychosis, hysteria, ulcers and wounds[14]. it has therapeutic properties, such as sedative, carminative and antispasmodic properties; it was used for treatment of headache, rheumatism, indigestion and hypersensitivities [15].

It was commonly used for its anti-angiogenic[16],antioxidant[17-23] , antimicrobial[24, 25] , anticancer[26-30], Antidysrhythmic[31] anti-stress and anti-anxiolytic [32-36],anti-herpes and anti-viral[37-45]anti- tumor, anti-Alzheimer[11, 46-51], anti-diabetic [52],antidepressant[53, 54] anti-cardiovascular diseases [54-57],memory improving [51, 58],anti-HIV[59],anti-inflammatory[60].It was said to be good for insomnia and dyssomina[61-63], concentration [64], antihyperlipidemic activities and effects [65].

Chemical compounds

the main constituent of the lemon balm were shown to be hydroxycinnamic acid derivatives, particularly rosmarinic acid, caffeic acids, chlorogenic acid, and metrilic acid[66-71] ,tannins[72-76], flavonoids, including luteolin, luteolin 7-O-beta-D-glucopyranoside, apigenin 7-O-beta-D-glucopyranoside, and luteolin 3-O-beta-D-glucuronopyranoside[77-83], monoterpene glycosides[84], sesquiterpenes, including β-caryophyllene and germacrene[84]triterpenes[85]and volatile oils, including citronellal, citral a (geranial), citral b (neral), methyl citronellate, ocimene, citronellol, geraniol, nerol, β-caryophyllene, β-caryophyllene oxide, linalool, and ethric oil[79, 80, 86-90] .

The volatile oil comprises 0.5-0.1% of the plant by weight, and citronellal, geranial, and neral constitute about 50-70% of this oil[86]. Eugenyl glycoside has been isolated from lemon balm leaves[91]. The chemical composition of lemon balm tea yielded 10 mg/L of essential oil (74% citral)and large amounts of polyphenol compounds[92]. Steam distillates of lemon balm callus cultures yielded dehydroabietane and another diterpene hydrocarbon, with the relative proportion of those two compounds varying considerably during cultivation passage[93].

The constituent of the essential oil of the plant in various climates is different, but citral(geranial and neral), citronellal, geraniol are main components. Many parameters influencing essential oil composition and yield, such as light intensity, nutrient, temperature, cultural practice genotype, plant part age, harvesting time[94]. The chemical composition of the essential oil of the plant leaf has also been studied. The major compounds were citronellal, citral and β-caryophyllene. Citral is a mixture of two monoterpenes, geranial and neral. Due to its intense lemon aroma and flavour, citral is used widely in foods and cosmetics[95].Also some flavonoids such as luteolin-7-o-glucoside(0.0002%).The lemon balm extract contained hydroxycinnamic acid derivatives and flavonoids with caffeic acid, m-coumaric acid,eriodictyol-7-O-glucoside, naringin, hesperidin, rosmarinic acid, naringenin, hesperetin being identified[96].

Mechanisms of action

Lemon balm has shown to possess high phenolics content and antioxidant properties[97].Lemon balm extracts and rosmarinic acid have both been demonstrated to enjoy antioxidant properties in vitro[4, 66, 70], and rosmarinic acid and caffeic acid have demonstrated significant antioxidant and immune modulating activities[70, 71, 98-100]. During linoleic acid autoxidation and its EDTA-mediated oxidation, lemon balm showed antioxidant activity[101]. Some other antioxidant activity of lemon balm has been shown as evidenced by the reduction of 1,1-diphenyl-2-picrylhydrazyl(DPPH)[102]. Studies have demonstrated that the cytoprotective effect of lemon balm extracts seen in rats was partly due to [92]free-radical scavenging properties[77, 98] .Immunostimulation effects of a lemon balm extract were also demonstrated[103]. Inhibitory effects of rosmarinic acid from lemon balm on porcine pancreatic amylase were reported in vitro[104].

A novel pharmacological mechanism of action for the anxiolytic botanical *Melissa officinalis* L. (lemon balm) is reported. The methanol extract was identified as a potent in vitro inhibitor of rat brain GABA transaminase (GABA-T), an enzyme target in the therapy of anxiety, epilepsy and related neurological disorders. Bioassay-guided fractionation led to the identification and isolation of rosmarinic acid [RA] and the triterpenoids, ursolic acid (UA) and oleanolic acid (OA) as active principles. Phytochemical characterization of the crude extract determined RA as the major compound responsible for activity (40% inhibition at 100 microg/mL) since it represented approximately 1.5% of the dry mass of the leaves. Synergistic effects may also play a role[105].

Antiherpes and anti-HIV effect

the virucidal and antiviral effects of *Melissa officinalis* L. extracts (M1, M3, M3 and M4) with respect to Herpes simplex virus type 1 was investigated and it was demonstrated that there was no significant values of inhibiting activity of M1, M2, and M3 on the same virus in vitro or in vivo. Caffeic, rosmarinic and ferulic acids contribute to antiviral activity of M. officinalis L. [44]. In an in vitro study, anti-herpes activity of Melissa officials was investigated and it was suggested that the Melissa extract demonstrated a high virucidal activity against HSV-1, even at very low concentrations of 1.5 µg/ml. [41]. A hydroalcoholic extract of lemon balm leaves was investigated against the Herpes simplex virus type 2 (HSV-2) in comparison with acyclovir. Lemon balm showed to reduce the cytopathic effect of HSV-2 on Vero cells, in the range of non-toxic concentrations [38].

A specially prepared dried extract from Melissa leaves was investigated in a double-blind study and the antiviral activity of this plant against herpes simplex infections was in vitro confirmed. Besides, the treatment with this plant was shown to be effective at very early stages of the infection [43].A double-blind, placebo-controlled, randomized trial was carried out with the aim of proving efficacy of standardized balm mint cream for the therapy of herpes simplex labialis. The tested formulation is effective for the treatment of herpes simplex labialis[42]. Aqueous extracts from leaves of this plant were examined for its inhibitory effect against immunodeficiency virus type 1 (HIV-1) in a clinical trial study. Aqueous extracts from Lamiaceae was found to reduce the infectivity of HIV-1 virions at non-cytotoxic concentrations rapidly. Its mechanism of action seems to be its enhancement of the virion's density before its surface engagement [59].

In an animal study, the antiviral effect of lemon balm oil of *Melissa officinalis*, on herpes simplex virus (HSV-1)(HSV-2)was examined and it was suggested that Melissa oil affected the virus before adsorption, but not after penetration into the host cell, thus lemon balm oil is capable of exerting a direct antiviral effect on herpes viruses[40].

Antioxidant effects

The leaf material of lemon balm was extracted and was investigated for potential in vitro antioxidant properties. It was demonstrated that the lemon balm extract has the ability to scavenge both synthetic and natural free radicals. This is of significant importance as it indicates that the extract may have the potential to prevent oxidative damage in vivo by preventing free radical-mediated oxidative stress. Due to its iron (II) chelating activity of the extract, its antioxidant potential was increased[96].

Lemon balm was analyzed to determine their antioxidant activity and content of total phenolics, L-ascorbic acid, and carotenoids. The ability to scavenge the free radical DPPH (2,2-diphenyl-1-picrylhydrazyl) was very high in almost all tested samples[106].

In an animal study, the efficacy of aqueous extract of *Melissa officinalis* was investigated in decreasing manganism - induced brain oxidative stress in mice. The results was indicated that M. officinalis aqueous extract possesses potent antioxidative and neuroprotective properties, validating its efficacy in attenuating Mn-induced oxidative stress in the mouse brain[107]. Antioxidant activity of this plant was examined in lots of other studies and was confirmed [20, 108].

Anti- Alzheimer and Neuroprotective Effects

The efficacy of Melissa aromatherapy in the treatment of patients with Alzheimer's disease was assessed in a blinded randomized controlled trial comparing it with donepezil. It was shown that there is no evidence that Melissa aromatherapy has priority to donepezil in this case. Nonetheless, the remarkable improvement in the placebo group emphasizes the potential non-specific benefits of this plant in the treatment of these patients.[109]**.**

In another study, the acute effects on cognition and mood of a standardized extract of M. officinalis was investigated. It was demonstrated that utilizing the cognitive factors previously derived from the CDR battery, included a sustained improvement in Accuracy of Attention following 600 mg of Melissa and time- and dose-specific reductions in both Secondary Memory and Working Memory factors. Self-rated "calmness," as assessed by Bond-Lader mood scales, was elevated at the earliest time points by the lowest dose, whilst "alertness" was significantly reduced at all-time points following the highest dose. Both nicotinic and muscarinic binding were found to be low in comparison to the levels found in previous studies.[36].

The efficacy and safety of *Melissa officinalis* extract using a fixed dose (60 drops/day) in patients with mild to moderate Alzheimer's disease were examined. At four months, *Melissa officinalis* extract produced a significantly better outcome on cognitive function than placebo. There were no significant differences in the two groups in terms of observed side effects except agitation, which was more common in the placebo group [p = 0.03].thus, it was concluded that *Melissa officinalis* extract is of value in the management of mild to moderate Alzheimer's disease and has a positive effect on agitation in such patients[110]**.**

In another study, cholinergic antagonists were recorded for their amnesic and dementia-inducing properties of Melissa were examined[111]**.**The extract of *Melissa officinalis* have been studied on the amelioration of Alziethmer symptoms. The mechanisms involved in this amelioration of this disease including acetylcholinesterase(AChE) inhibition, modification of monoamines, antiamyloid aggregation effect, and antioxidant activity were summarized in a study and the anti- Alzheimer effect of Melissa was confirmed[48]. *Melissa officinalis*, extracts have been demonstrated to be useful for dementia, both alone or in combination[34]. The possible neuroprotective effects of total ethanolic extract, acidic and nonacidic fraction of *Melissa officinalis* on Aβ-induced cytotoxicity and oxidative stress in PC12 cells were assessed and also their in-vitro anticholinesterase activity were measured.

Theprotective effects of *Melissa officinalis* total extract and acidic fraction were not attributed to their anticholinesterase activity. Acidic fraction showed more potent protective effect compared to the total extract, leading to the fact that polyphenolic compounds and terpenoic acids were the most effective components in the total extract concentrated in this fraction[46].Effect of *Melissa officinalis* on hypoxia induced neuronal death in a cortical neuronal culture system as in vitro model and transient hippocampal ischemia as in vivo model was investigated. Results showed that *Melissa officinalis* could be considered as a protective agent in various neurological diseases associated with ischemic brain injury[47].The neuroprotective effects of *Melissa officinalis* was investigated against neuron toxicity in hippocampal primary culture induced by 3,4-methylenedioxymethamphetamine (MDMA) or ecstasy. A high dose of ecstasy caused profound mitochondrial dysfunction, around 40% less than the control value, and increased apoptotic neuronal death to around 35% more than the control value in hippocampal neuronal culture. Co-treatment with *Melissa officinalis* significantly reversed these damages to around 15% and 20% respectively of the MDMA alone group, and provided protection against MDMA-induced mitochondrial dysfunction and apoptosis in neurons. *Melissa officinalis* has revealed neuroprotective effects against apoptosis induced by MDMA in the primary neurons of hippocampal culture, which could be due to its free radical scavenging properties and monoamine oxidase (MAO) inhibitory effects[49].Both methanolic and aqueous extracts of this plant were tested for protective effects on the PC12 cell line, free radical scavenging properties and neurological activities. The results suggest that the plant has a significant ($P < 0.05$) protective effect on hydrogen peroxide induced toxicity in PC12 cells. No activity was detected in the acetylcholinesterase and GABA assays. The methanolic extract was more effective than the aqueous [11].

Anti-depression and anti-anxiety

The antidepressant-like activity of water extract of this plant was investigated by evaluating its influence on the behaviors and the relevant neurotransmitters of rats performed to force swimming test[53].

The behavioral effects of an acute or subacute orally administered *M.officinal* is ethanol extract were evaluated in male and female Wistar rats in elevated plus-maze, forced swimming and open field tests. The effects of diazepam and fluoxetine were also assessed. The potential psychoactive properties of M. officinalis may provide a unique pharmacological alternative for certain psychiatric disorders; however, the efficacy seems to be dependent on both gender and administration length[54].

Ina double blind randomized placebo-controlled clinical trial, the efficacy and safety of the dried extract of M. officinalis was evaluated on adults suffering from benign palpitations. Results showed that 14-day of treatment with lyophilized aqueous extract of M. officinalis leaves reduced frequency of palpitation episodes and significantly reduced the number of anxious patients in comparison to the placebo. Besides, M. officinalis extract showed no serious side effects.it can be concluded that Lyophilized aqueous extract of M. officinalis leaves may be a proper and safe herbal drug for the treatment of benign palpitations [55].

Chronic administration of *Melissa officinalis* L. was shown to relieve stress-related effects [33].in addition, in another study, the effects of chronic administration of *Melissa officinalis* L. extract (Cyracos, Naturex)was

investigated and it was show that Cyracos has anxiolytic-like effects under moderate stress conditions and does not alter activity levels[112]

Melissa officinalis (lemon balm) and Valeriana officinalis (valerian)have been illustrated to decrease laboratory induced stress. These results suggest that a combination of *Melissa officinalis* and *Valeriana officinalis* possesses anxiolytic properties in a dose-dependent manner; however, it needs further study[113].

Anti-agitation

Melissa officinalis was shown to inhibit binding of t-butylbicyclophosphorothionate to the rat forebrain gamma-aminobutyric acid receptor channel, but had no effect on N-methyl-D-aspartate, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropianate or nicotinic acetylcholine receptors. Thus, MO cause a significant dose-dependent reduction in both inhibitory and excitatory transmission, with a net depressant effect on neurotransmission that is in contrast to the classical GABA antagonist picrotoxinin which evoked profound epileptiform burst firing in these cells. The anti-agitation effects in patients and the depressant effects of MO in in-vitro we report in neural membranes are unlikely to reflect a sedative interaction with any of the ionotropic receptors[114].

It was suggested that leaves of *Melissa officinalis* L. increases cell proliferation, neuroblast differentiation and integration into granule cells by decreasing serum corticosterone levels as well as by increasing GABA levels in the mouse DG [30].

Antimicrobial and antifungal

The essential oil obtained from leaves of *Melissa officinalis* L. was investigated for its in vitro antimicrobial activity. The results showed that the essential oil presented high antimicrobial activity against all microorganisms targeted mainly against five human pathogenic bacteria, one yeast *Candida albicans* and two phytopathogenic fungi tested. [115].in addition, antimicrobial of *Melissa officinalis* essential oil was investigated and it was shown that the most effective antibacterial activity was expressed on a multiresistant strain of Shigellasonei. A significant rate of antifungal activity was exhibited on Trichophyton species [25].besides, the antimicrobial properties of essential oil from romanian *Melissa officinalis* were assayed and it was shown a high activity against Candida albicans. The gram-negative bacteria were not affected by the lemon balm oil [24].furthermore, antimicrobial activities of the extracts and rosmarinic acid of this plant were evaluated and were confirmed [116].

Insomnia

Efficacy and tolerability of a combined valerian/lemon balm preparation were investigated in an open, multicenter study in children less than 12 years suffering from restlessness and nervous dyskoimesis. Euvegal forte was effective in the treatment of younger children with restlessness and dyssomnia and it was very well tolerated [62].For the first time, it has been shown that chronic administration of *Melissa officinalis* L. relieves stress-related effects. It is essential that more studies incorporate a placebo and investigate physiological stress markers[33].

Anticancer

The antiproliferative and proapoptotic effects of ethanolic leaves extract of *Melissa officinalis* were investigated in human coloncarcinoma cells.it found that Melissa officinalis extract inhibits the proliferation of colon carcinoma cells and induces apoptosis through formation of ROS[29].the selective anticancer effects of an MO extract (MOE)was investigated in different human cancer cells. Results indicated that a hydro-alcoholic extract of MO possess a high potency to inhibit proliferation of different tumor cells in a dose independent manner, suggesting that an optimal biological dose is more important than a maximally tolerated one. Moreover, the antiproliferative effect of MO seems to be tumor type specific, as hormone dependent cancers were more sensitive to antitumoral effects of MOE[117].the activity of the M. officinalis essential oil (EO) and its major component (citral) in GBM cell lines was examined . Both EO and citral decreased the viability and induced apoptosis of GBM cells as demonstrated by DNA fragmentation and caspase-3 activation. the results show that EO, through its major component, citral, may be of potential interest for the treatment of GBM[28].it also was suggested that MOE increases cell proliferation, neuroblast differentiation and integration into granule cells by decreasing serumcorticosterone levels as well as by increasing GABA levels in the mouse DG[30].

Anti-inflammatory

The effect of the essential oil of the leaves of this plant was investigated for anti-inflammatory properties by using carrageenan and experimental trauma-induced hind paw edema in rats. M. officinalis L. essential oil showed

remarkable reduction and inhibition of edema induced by carrageenan at 6 h at 200 and 400 mg/kg with 91.66% and 94.44%, respectively (P < 0.001). thus, it can be concluded that the essential oil of M. officinalis L. had potential anti-inflammatory activities [60].

Cardiovascular disease

In a double blind randomized placebo-controlled clinical trial, the efficacy and safety of the dried extract of M. officinalis on adults suffering from benign palpitations was evaluated. Fifty-five volunteers out of 71 recruited study subjects completed the trial. Results showed that 14-day of treatment with lyophilized aqueous extract of M. officinalis leaves reduced frequency of palpitation episodes and significantly reduced the number of anxious patients in comparison to the placebo .thus, it can be safely used for the treatment of benign palpitations [55].the influence of *Melissa officinalis* on cardiac conduction and susceptibility to lethal ventricular arrhythmia was assessed and it was shown that M. officinalis extract has a mild protective effect against reperfusion-induced lethal ventricular arrhythmias in rats[118].The effects of aqueous extract of *M. officinalis* aerial parts on Wistar rat heart with/without cardiac injury was examined and it was concluded that the lower dose of extract, by improving the balance of the redox system and by reducing the heart rate, may increase the heart resistance to injury. However, the higher doses of extract may intensify the injury of ischemic heart[57].

Memory and concentration improving

The role of cholinergic system on the memory improving activity of M. officinalis extract was investigated. These results suggest that M. officinalis can improve memory and that the cholinergic property of the extract may contribute to the memory-improving effects observed in this study. Then M. officinalis extract has potential therapeutic value in alleviating certain memory impairment observed in AD[58].

In a clinical trial, it was examined that whether treatment with a fixed combination of Valeria and Melissa may improve concentration, hyperactivity and impulsiveness. The fraction of children having strong/very strong symptoms of poor ability to focus decreased from 75% to 14%, hyperactivity from 61% to 13%, and impulsiveness from 59% to 22%. Parent rated social behavior, sleep and symptom burden showed highly significant improvements. Only in two children ,mild transient adverse drug reactions were observed[64].

Side effects:

no side effects have so far been reported for the herb [119] When used topically or orally in recommended doses [up to 30 days] in otherwise healthy adults and when consumed in amounts found in foods. Lemon balm has been assigned Generally Regarded as Safe (GRAS) status in the United States with a maximum level of 0.5% in baked goods.

• Possibly Unsafe: During pregnancy or lactation or in pediatric patients, and when used in patients with thyroid disorders or in combination with sedatives (theoretical)[120].

CONCLUSION

Melissa officinalis l. is widely used for therapeutic and non-therapeutic purposes that trigger its significant value. Various combinations and numerous medicinal properties of its extract, oil, and leaves demand further and more studies about the other useful and unknown properties of this multipurpose plant.

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