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Melissa officinalis and rosmarinic acid in management of memory functions and Alzheimer disease

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ABSTRACT

Alzheimer disease (AD) as worldwide progressive neurodegenerative disease is prevalent disease among elderly population. Due to limitation in chemical drugs along with their adverse effects of these treatments, research for finding more effective natural drugs, is one of interesting subjects among the scientists. *Melissa officinalis* (*M. officinalis*) has a long history of use in treatment of nervous system diseases. This review article evaluates the potency of *M. officinalis* in treatment of AD by review of experimental and clinical documents on the efficacy, safety and its mechanisms of action in management of AD. The information is extracted from electronic resources (PubMed, Wiley, Springer and Science Direct), English and Persian scientific books. In spite of different scientific and non-scientific reports on the use of *M. officinalis* and its main component of rosmarinic acid in neurodegenerative diseases, there is only one clinical trial on the efficacy of *M. officinalis* ethanol extract in management of AD. Different mechanisms of action for *M. officinalis*, including inhibitory effects against amyloid beta, reactive oxygen species, and acetylcholine esterase, are involved. Larger clinical trials are recommended to confirm the efficacy and safety of *M. officinalis* extracts in treatment of AD patients.

1. Introduction

Alzheimer disease (AD) as a progressive neurodegenerative disease is identified as a form of dementia. Ninety percent reduction in cholinergic neurons of AD patients is associated with low learning capacity and loss of cognitive functions[1]. β-amyloid plaques or amyloid-β (Aβ) peptides formation in brain's hippocampal area[2], disorder in acetylcholine neurotransmitter and reduction in acetylcholine in cholinergic function are involved in AD[3]. Increasing in acetyl cholinesterase (AChE) in AD is associated with breakdown of acetylcholine, which accelerates the development of AD. Furthermore, the anti-inflammatory function of acetyltransferase inhibitors is confirmed in inhibition of AD[4]. Oxidative stress, the aggregation of tau protein, excessive metal ions, and reduced acetylcholine levels are involved in AD. Oxidative stress disturbs the mitochondrial function, changes the metal homeostasis, and reduces antioxidant defense with potential effects on synapse, neurons, molecular targets, and cellular metabolism leading to production and accumulation of Aβ and hyperphosphorylated tau protein.

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Lifestyles and genetic factors are two other factors in AD[5].

The limited chemical drugs along with their reported adverse effects (diarrhea, vomiting, fatigue, nausea, weight loss, loss of appetite) are the main reasons for finding the natural effective treatments by scientists.

Different herbal prescriptions are used for prevention and treatment of AD in traditional systems. In Iranian Traditional Medicine, the cold and dry subdivision of "Nesyan" (forgetfulness) is equal to AD[6] and Iranian traditional practitioners used different plants[6] including *Melissa officinalis* (*M. officinalis*), *Crocus sativus*, *Boswellia serrata* and *Nigella sativa* for improving the memory function and treatment of AD[7]. There are two review articles on phytochemistry and pharmacology effects of *M. officinalis* with no consideration to its effect on memory function[8,9]. This article evaluates the pharmacological, clinical and toxicological aspects of *M. officinalis* and its main component rosmarinic acid in management of AD and memory.

2. *M. officinalis* in different traditional systems

M. officinalis (lemon balm) is a perennial herb, native to Mediterranean regions and Southern Europe. Melissa as a Greek word means honeybee, which attracts the bees to its flavor. *M. officinalis* is traditionally used from ancient times. Dioscorides applied it as analgesic and anti-scorpion bites agents. Furthermore, its other traditional uses are for heart diseases, earache, morning sickness, toothache and wounds and it is known as a good preventive agent for baldness, catarrh, fever, and flatulence. In Europe, its tea is used as general relaxant drink, sleep aid, mental stress and carminative agent for mild gastrointestinal disorders. *M. officinalis* essential oil is applied as antiseptic agent and dressing the surgical wounds. The clinical approvals for *M. officinalis* in treatment of herpes labialis, gastrointestinal disorders and sleep disturbances are present. In folk medicine, it is recommended for treatment of amenorrhea, asthma, cough, bee sting, dizziness, migraine, dysmenorrhea, headache, tachycardia, tracheobronchitis and urinary incontinence[10]. In Portugal, *M. officinalis* decoction, or infusion with Portuguese local name "Erva cidreira" is used for management of nervous problems, insomnia, memory loss, intestinal inflammatory diseases, sea sickness, renal and gall bladder ailments. The efficacy of *M. officinalis* on nervous system dates back to 50-80 BC, and Paracelsus (1493-1541) recommended it for all nervous systems' complaints and as general tonic for brain and memory[11–13]. John Evelyn (17th century) stated that "Balm is sovereign for the brain, strengthening the memory and powerfully chasing away melancholy". Daily administration of canary wine containing *M. officinalis* essential oil is believed to strengthen the brain and renew youth. Thomas Coghan (1584) recommended his students to drink *M. officinalis* tea to clear head, increase the memory and sharpen the memory[14]. The pillow full of dried *M. officinalis* leaves is used to induce relaxing sleep. *M. officinalis* has license in Germany as standard medicinal tea to induce the sleep. European Commission approves the use of *M. officinalis* for nervous sleeping disorders[15]. European Scientific Cooperative on Phytotherapy (ESCOP) recommends it for tenseness, restlessness and irritability disorders[16]. According to Health Canada, *M. officinalis* is used as sleep aid for restlessness and insomnia due to mental stress[17].

3. Main chemical compositions of *M. officinalis*

Essential oil (0.1%-0.5%), flavonoids (glycosides of luteolin, apigenin, quercetin, kaempferol)[18], monoterpene glycosides, polyphenols (rosmarinic acid, chlorogenic acid, caffeic acid, hydroxyl cinnamic derivatives) and triterpenes (ursolic and oleanolic acids) were found in *M. officinalis* as main chemical compounds[19]. Citronellal, geraniol, isogeraniol, geraniol acetate, nerol acetate, caryophyllene and β-caryophyllene oxide were reported as main components of its essential oil[20].

4. Clinical studies on efficacy of *M. officinalis*

4.1. M. officinalis in treatment of AD

Bioinformatics' resources and methodological analysis of medicinal plants and their ingredients with clinical trials on AD showed that *Ginko biloba*, *M. officinalis*, *Salvia officinalis*, *Huperzia serrata* had anti-AD effects. Analysis of these plants from the target network perspective suggested *Huperzia serrata* had anti-AD effects, through a symptom improving way, *Salvia officinalis* targeted the inflammation associated pathways, while, *Ginko biloba* and *M. officinalis* targeted the fundamental pathways of AD[21].

Two clinical investigations confirmed the potency of *M. officinalis* in treatment of AD. In the first parallel, randomized, placebo-controlled study, the efficacy and safety of 60 oral drops of *M. officinalis* ethanol extract (45%; 1:1, standardized to 500 μg citral in each mL) for 4 months were evaluated on 42 participants (65-80 years old) with mild to moderate AD. There was no significant difference between two groups in regard of sex/gender distribution (9 female, 12 male), and age (73.00±3.84 *vs*. 73.71±3.71 in intervention and control groups, respectively). The cognitive subscales of Alzheimer's disease Assessment Scale (ADAS-cog) and Clinical Dementia Rating-Sum of the Boxes (CDR-SB) scores were evaluated as two main efficacy measures. Six domains of judgment, memory, orientation, problem solving, community affairs, home, hobbies, and personal care were evaluated by CDR-SB scores. Thirty five patients completed the study. One and six patients left the study from *M. officinalis* and placebo groups, respectively. *M. officinalis* caused a significant improvement in cognition after 4 months of treatment. Improvement was observed on ADAS-cog and CDR-SB scores. After eight weeks of treatment, CDR-SB score significantly reduced in comparison with placebo group (P<0.000 1). After 16 weeks of treatment with intervention drug, the severity of symptoms (P<0.000 1), and ADAS-cog score (P=0.000 1) significantly decreased in comparison with placebo group. Although, there was insignificant difference in the frequency of adverse effects (vomiting, nausea, dizziness, wheezing,

and abdominal pains) between two groups, the frequency of agitation was higher in the placebo than *M. officinalis* groups in patients with AD[22,23].

According to results of these clinical studies, *M. officinalis* extract not only inhibited the progress of severity symptoms, but also caused a significant reduction in agitation of patients with AD. Agitation as common ailment in AD and other dementias is associated with severe adverse consequences in patients and their relatives[24]. The effects of *M. officinalis* on agitation may be related to its essential oil.

In double blinded placebo controlled study, *M. officinalis* essential oil with main components of citronellol (22%), caryophyllene (18%), neral (7%), geraniol (7%), geranyl acetate (3%) and citronellal (4%) on agitation in severe dementia of 72 patients with mean age of (78.5±8.1) years (77.2 melissa, 79.7 placebo), exhibited that topical administration of 200 mg of *M. officinalis* essential oil or placebo (sunflower) on patient's faces and arm twice daily by caregiving staff along with psychotropic agents improved significantly agitation (CMAI) score and quality of life indices (QLI) over 4 weeks of treatments. A total of 60% (21/35) patients with *M. officinalis* essential oil and 14% (5/36) of patients with placebo all showed 30% reduction in CMAI score. The corresponding overall improvement in agitation score was recorded for 35% and 11% of patients of two groups, respectively. The significant difference was observed among two groups in regard of CMAI score and overall improvement in agitation (P<0.001). QLI was improved significantly much more in *M. officinalis* essential oil than placebo group (P=0.001)[11].

4.2. Efficacy of M. officinalis on memory of healthy participants

The effect of single doses of encapsulated dried leaf extract of *M. officinalis* (600, 1 000, 1 600 mg) on mood modulation and cognitive performance of 20 healthy young participants (18-23 years old, mean age 19.2 years) was the subject of randomized placebo-controlled double blind balanced crossover study. The cholinergic receptor binding properties of *M. officinalis* and the improvement in mood, cognitive performance and calmness in dose and time dependent manner were confirmed after ingestion of different single doses of *M. officinalis*. The profile of results for 1 600 mg of *M. officinalis* extract was favorable, but increasing the dose reduced the speed of time memory task performance and the rapid visual information processing task during the study[25]. So, *M. officinalis* may have the potency for improving the memory in healthy peoples.

5. Mechanisms of action of *M. officinalis* potency in memory functions and AD

5.1. Effect of M. officinalis on AchE

One pathological factor for AD is deficiency in acetylcholine neurotransmitters and reducing acetylcholine in cholinergic system with critical role of AChE.

Intra-peritoneal injection of *M. officinalis* leaves ethanol extract alone, or in combination with scopolamine in rat animal model reduced AChE enzyme in hippocampus of rats in comparison with scopolamine, and normal saline treated rats[26], which implies its inhibitory effect against AChE. Morris water maze showed that after oral administration of *M. officinalis* ethanol extract, male Wistar rats with streptozotocin induced spatial memory deficit had reduction trend in speed and study time, which showed a significant reduction in amyloid plaques of CA1 hippocampus of *M. officinalis* treated rats[27]. Rosmarinic acid, and its derivatives are known as responsible agent for anti-AChE activity of *M. officinalis* extracts[28]. Sub-chronic administration of standard *M. officinalis* leave ethanol extract with rosmarinic acid improved behavioral and cognitive response of scopolamine treated rats. *M. officinalis* had strong inhibitory effects on AChE and butyryl cholinesterase mRNA level in the brain and reducing effect on *BACE* mRNA expression in frontal cortex and hippocampus. Rosmarinic acid had strong stimulatory effect on butyryl cholinesterase in the hippocampus[29]. *M. officinalis* extract increased the latency of reaction vertical movements and locomotor activity in passive avoidance test[30]. Oral administration of rosmarinic acid improved cognitive function, learning and memory in scopolamine treated rats and this effect was similar to donepezil in improvement of acquisition, however, the ameliorative effect of donepezil on memory retention was higher than rosmarinic acid. The anti-cholinergic effect of scopolamine caused the inhibition on central cholinergic neuronal activity and impaired cognition function, learning and memory. Also, rosmarinic acid improved memory and passive avoidance learning of normal rats[31]. The cognitive enhancing effect and weak ameliorating effects of sub-chronic administration of rosmarinic acid in acute phase of treatment were observed in animal model[32]. Rosmarinic acid could be detected in the brain, 30 min after administration[33]. Rosmarinic acid with different sites of attachment to acetylcholine esterase from donepezil[31] increased the acetylcholine content and reduced the cholinesterase in the brain of mice[34]. *M. officinalis* had acetylcholine receptor with nicotinic and muscarinic binding properties in central nervous system[14,35].

M. officinalis improved the cholinergic system of scopolamine memory impairment and acetylcholine esterase in rats[36]. The acetylcholine esterase inhibitory effect was reported for *M. officinalis* decoction and its essential oil[37]. The neuro-protective effect of *M. officinalis* extract was probably attributed to inhibition of pro-inflammatory cytokines like IL-1, TNF-α from activated neurons, astrocytes, endothelial cells and microglia inhibited astrogliosis and changed the matrix metalloprotease in rat animal model[38].

5.2. Effects of M. officinalis on amyloid beta

β-amyloid formation is one of the reasons that exacerbate the AD. The neurodegenerative process in AD is attributed to oxidative stress. β-amyloid significantly increases the free radicals and their products and enhances the production of peroxynitrite ($ONOO^-$) and peroxidation of membrane lipid, which are associated with degeneration of neurons and cell death in AD. $ONOO^-$ is produced in the brain of AD as the result of β-amyloid formation in senile

plaque[34]. β-amyloid related reactive oxygen species and formation of β-amyloid fibrils are inhibited by rosmarinic acid *in vitro* experiments[39]. Also, rosmarinic acid destabilizes the created β-amyloid fibrils[40]. Rosmarinic acid had protective effects on A β_{25-35} memory impairment of short and long term memory in mice model[41]. Rosmarinic acid, and their metabolites (hydroxyphenyl propionic acid, caffeic acid, and ferulic acid) inhibited the release of NO in macrophages and activated astrocytes[42,43] and β-amyloid formation[44,45]. Rosmarinic acid protects the cells against β-amyloid induced toxicity, inhibits the phosphorylated p38 mitogen activated protein kinase and reduces the membrane lipid peroxidation in a dose dependent manner. Rosmarinic acid inhibits the hyper phosphorylation of tau protein through the inhibition of p38 MAP kinase pathway and protects against β-amyloid induced apoptosis by inhibition of the caspase-3 activity and DNA fragmentation[39].

5.3. Effects of *M. officinalis* on ROS

The high amounts of potent antioxidant and phenolic compounds (hydroxycinnamic derivatives, rosmarinic acid, chlorogenic acid, caffeic acid) in *M. officinalis* confirmed its antioxidant activity[9]. The antioxidant activities of *M. officinalis* essential oil, ethanol extracts and its decoction, rosmarinic acid, chlorogenic acid, and caffeic acid have been exhibited in DPPH and total antioxidant capacity systems[37]. *M. officinalis* decoction improved the oxidative stress, and plasma levels of oxidative enzymes (catalase, superoxide dismutase, glutathione peroxidase, and superoxide dismutase). Also a reduction was caused in plasma DNA damage, myeloperoxidase and lipid peroxidation[46]. *M. officinalis* essential oil increased the antioxidant capacity of injured hippocampus ischemic brain, and inhibited the malondialdehyde production in rat's brain[47]. *M. officinalis* ethanol extract reversed the harmful effects of ethanol or nicotine on memory and learning[48]. Moreover, the anti-inflammatory effects of *M. officinalis* extracts[49,50], and rosmarinic acid[51] are other probable mechanisms for its efficacy in AD (Figure 1).

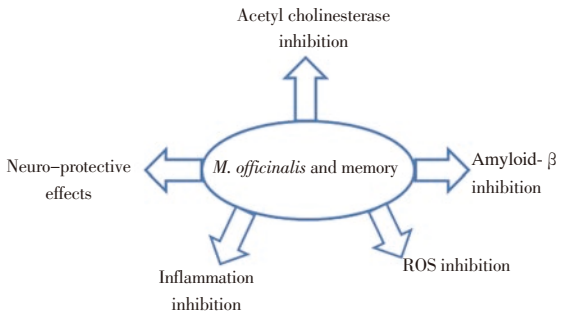

Figure 1. Mechanisms of action of *M. officinalis* potency in memory functions and Alzheimer disease.

6. Safety and recommended dose

Intra-peritoneal daily injection of 450 and 1 350 mg/kg of *M. officinalis* ethanol extract (70%) for two weeks in BALB/c mice reduced alkaline phosphatase and alanine aminotransferase, dose dependently in comparison with control group. *M. officinalis* extract had no effect on creatinine and urea. A mild polymorphism in hepatocytes and moderate necrosis in liver parenchymal, sinusoids dilation and apoptosis were observed in comparison with other groups. Secretion of mononuclear inflammatory cells in portal space, liver parenchymal necrosis and irregular hepatocyte plates were found in microscopic examinations. Thus, the extract at the dose of 1 350 mg/kg extract had acute toxicity on kidney[52].

Administration of 450 and 1 350 mg/kg of *M. officinalis* aqueous extract for 30 d significantly reduced the liver enzymes and increased the total protein and urea in *M. officinalis* treated rats. Pathological examination of liver showed tissue damage in dose dependent manner. Therefore, *M. officinalis* aqueous extract was toxic to liver cells[53].

The safety evaluations of clinical trials[22,23] on *M. officinalis* exhibited that it is generally well tolerated and there is no contraindication at recommended doses, but it is not recommended to use in hyperthyroidism due to its thyroid inhibitory effects. The safety, tolerability and pharmacokinetics of single dose of *M. officinalis* extract (standardized to 500 mg rosmarinic acid) in fasted and fed states of healthy individuals showed that after 1 h, the serum concentration of rosmarinic acid was 162.2 nmol/L in fasted state. Serum concentration and rosmarinic acid absorption were increased by food intake. Rosmarinic acid was not detected in blood cell function parameters, kidney and liver. The treatment was safe and well tolerated in healthy patients[54].

The administration and tolerance of *M. officinalis* extract were also confirmed in pediatric populations[55]. Aromatherapy with *M. officinalis* oil in patients with severe dementia is well tolerated[11]. Due the lack of sufficient data, it is not recommended during lactation and pregnancy.

The daily oral dose of dried herb for adult is 1.5-4.5 g, as infusion in 150 mL water, 2-4 mL of 45% ethanol extract (1:1), three times a day, and 2-6 mL tincture (1:5 in 45% ethanol), three times a day[56].

According to the Iranian Traditional Medicine, the typical dose for *M. officinalis* was 40 g dry leaves, 80 g fresh leaves and 9 g dry seeds[57,58]. Doses of its extract at 600-1 600 mg are used in clinical studies. The topical agents containing 1% *M. officinalis* extract are used for treatment of herpes virus lesions[59].

7. Conclusion

M. officinalis as herbal medicine is popular in different systems of medicine. Although, *M. officinalis* is used not only as sleep aid and anti-herpes labialis agent, but also as complementary treatment for AD and enhancing the memory. The results of clinical studies have showed *M. officinalis* ethanol extract and rosmarinic acid can act *via* diverse mechanisms to help patients with AD. It can trigger multiple targeted agents involved in AD and inhibit the acetylcholine esterase activity and β-amyloid plaque formation in brain. Also, it has anti-

inflammatory effect and neuro-protective effects by its antioxidant activities. The role of *M. officinalis* ethanol extract, essential oil and rosmarinic acid in reduction of agitation has already been confirmed in patients with AD in previous studies. Reduction of agitation in patients has occurred after decreasing the locomotor activity. In conclusion, *M. officinalis* essential oil is recommended for further clinical study due to its low yield and price. More large clinical trials on *M. officinalis* ethanol extract along with other famous medicinal plants in AD are needed in order to overcome the limitation of current studies.

Conflict of interest statement

The author has no competing interests to declare.

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