

Mini review



Melissa officinalis: a memory enhancer remedy

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Abstract

Melissa officinalis (MO) is a perennial herb and it is a member of Lamiaceae family. MO is native to Europe and the leaves of the plants are used in traditional medicine for its effects on the central nervous system functions such as sedation, anxiolytic and memory enhancement. Furthermore, MO has antioxidant and anti-inflammatory effects. Convincing evidence shows that molecular changes such as oxidative stress and inflammation are associated with a decline in cognitive abilities, including learning and memory. MO and its main ingredient, rosmarinic acid, possess robust antioxidant and anti-inflammatory effects. Besides, animal model studies have shown that MO and rosmarinic acid can improve memory loss in Alzheimer's disease. In this review beneficial implications of MO have been discussed.

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Introduction

Melissa officinalis L. (MO), also known as lemon balm, is used in traditional medicine for its effects on central nervous system (CNS) functions (Shakeri et al., 2016) such as sedation (Ghazizadeh et al., 2020) and memory-enhancement (Dehbani et al., 2019). There is a growing body of research that indicates beneficial implications of MO in treatment of diseases including diabetes (Khodsooz et al., 2016) and Alzheimer's disease (AD) (Akhondzadeh et al., 2003). Furthermore, MO has antioxidant (Alizadeh Behbahani et al., 2019), antimicrobial (Hassan et al., 2019) and anti-inflammatory (Bounihi et al., 2013) effects. Rosmarinic acid as the main active substance in MO is an ester of caffeic acid and 3, 4-dihydroxyphenyllactic acid (Petersen and Simmonds, 2003). Learning and memory are the supreme

functions of CNS (Kandel, 2001). Memory has been divided into two distinct stages: short-term memory and long-term memory, which its formation requires de novo transcription and protein synthesis (Eivani et al., 2019). In this review, we discuss the potential effect of MO on memory formation and memory impairment.

***Melissa officinalis* and memory**

There is a growing tendency for memory-enhancing medicinal herbs (Jivad and Rabiei, 2014). MO is one of the medicinal herbs frequently used for memory enhancement. In an animal study, chronic (14 days) oral administration of MO hydro-alcoholic extract (50, 100 and 200mg/kg) was shown to augment the learning and memory in the passive avoidance task in adult rats (Dehbani et al., 2019). MO also, can improve memory function in healthy individuals, the

Table 1: Memory enhancement effect of MO and rosmarinic acid in animal models of Alzheimer's disease

Treatment	Route of administration	Model	Test	Reference
RA	IP	ICV injection of A β	Y-maze test Novel object recognition task	Alkam et al., 2007
RA	IP	intrahippocampal injection of A β	Y-maze test passive avoidance test	Baluchnejadmojarad et al., 2013
HAMO	PO	ICV injection of A β	passive avoidance test	Beheshti and Shahmoradi, 2018
RA	PO	IP injection of Scopolamine	passive avoidance test	Hasanein and Mahtaj, 2015
HAMO	IP	IP injection of Scopolamine	Morris water maze	Soodi et al., 2013
HAMO	PO	ICV injection of STZ	Morris water maze	Sabbaghziarani et al., 2014

RA: rosmarinic acid, HAMO: hydro-alcoholic extract of *Melissa officinalis*, PO: gavage, IP: intraperitoneal injection, ICV: intracerebroventricular injection

results of a randomized, placebo-controlled, double-blind, balanced-crossover study conducted by Kennedy and colleagues in 2002 suggest that oral administration of a single dose of MO can modulate memory performance of healthy young volunteers in cognitive drug research computerized assessment test.

Melissa officinalis and memory impairment

Alcohol consumption affects the CNS, causing neuronal damage and a wide range of cognitive declines such as memory impairment (White et al., 2000). Research on laboratory animals has shown that chronic administration of rosmarinic acid prevents ethanol-induced amnesia in a dose dependent manner (Hasanein and Mahtaj, 2015).

Stroke is the fourth leading cause of death worldwide and the major cause of disability, ischemic injury is associated with inflammation and free radical metabolites (Kriz, 2006). It has been demonstrated that stroke can result in memory impairment (Kim et al., 2020) and the prevalence of post-stroke cognitive decline ranges from 20 to 80 percent (Sun et al., 2014). In a study carried out by Fonteles and colleagues in 2016, the effect of rosmarinic acid against memory deficits in ischemic mice was investigated. Their results revealed that rosmarinic acid inhibits the inflammatory response and prevents memory impairment induced by cerebral ischemia.

People worldwide are living longer, the proportion of older people has been increasing over the last century. A complication associated with age is

memory decline (Koen et al., 2019). In a randomized, parallel, double-blind, placebo-controlled clinical trial carried out by Taghizadeh et al. (2018) results indicated that MO could be beneficial for age-related memory impairments. They found that the chronic (one month) consumption of MO in combination with *Boswellia serrata* (a plant that produces frankincense) in participants led to a significant increase in memory compared to placebo.

Melissa officinalis and Alzheimer's disease

One of the most common type of dementia is AD. Approximately 70% of all dementia cases are recognized as AD. The most common risk factors for developing AD are age, genetic, vascular diseases and environmental factors. Prevalent and distinctive indications present within the patient's brain are the senile plaques and neurofibrillary tangles that are the result of the aggregation of two key molecules, tau and amyloid- β (A β) (Castellani et al., 2010). Animal models of AD comprise a group of inducible models with certain aspects of AD (Götz et al., 2018) such as intracranial injection of synthetic A β (Beheshti and Shahmoradi, 2018), intracranial and intraperitoneal injection of scopolamine (Aykaç et al., 2019) and intracranial injection of streptozotocin (Rostami et al., 2017; Grieb, 2016). Moreover, MO has been traditionally used for the treatment of dementia and AD, with the most characteristic manifestation of all dementia cases is the impairment of learning and memory. Animal model studies show that the hydro-alcoholic extract of MO can improve memory loss in

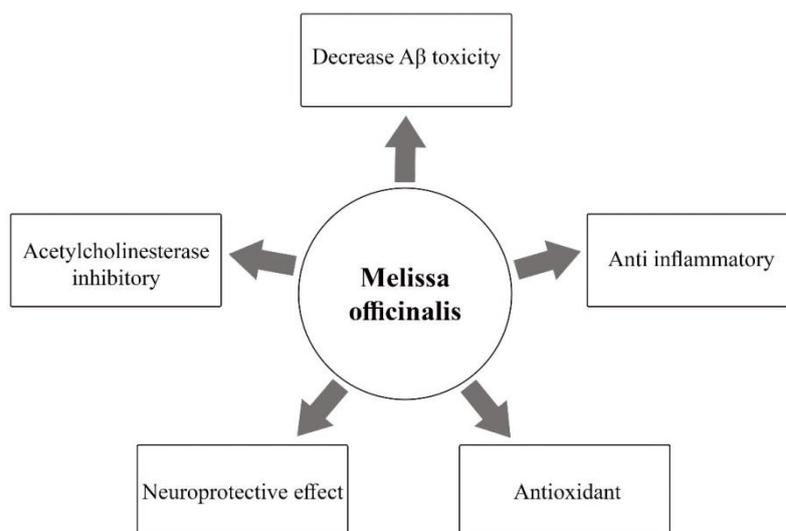


Fig.1. Possible mechanism of action of *Melissa officinalis* in memory enhancement.

AD (Table 1) (Beheshti and Shahmoradi, 2018; Sabbaghziarani et al., 2014; Soodi et al., 2014). Studies performed on rosmarinic acid as the main gradient of MO, also demonstrate memory enhancement effects in animal models of AD (Table 1) (Alkam et al., 2007; Baluchnejadmojarad et al., 2013; Hasanein and Mahtaj, 2015).

Evidence shows that molecular changes such as oxidative stress, precede the onset of clinical dementia (Wojsiat et al., 2018). Both the hydroalcoholic extract of MO (Koksal et al., 2011) and rosmarinic acid (Adomako-Bonsu et al., 2017) possess robust antioxidant properties. From another point of view, β -secretase is a key enzyme in the amyloidogenic pathway and its activity leads to the accumulation of neurotoxic forms of $A\beta$ (Hu et al., 2010; Venugopal et al., 2008). It was found that glycogen synthase kinase-3 β (GSK-3 β) has been actively involved with $A\beta$ toxicity and tau pathologies (Takashima, 2006) and that methanolic extract of MO has inhibitory effects on GSK-3 β and β -secretase (Gürbüz et al., 2019).

Acetylcholinesterase inhibitory effect of *Melissa officinalis*

One of the pathological factors of AD is the reduction of acetylcholine (ACh) neurotransmission in the brain areas dealing with learning and memory (Quirion, 1993). Acetylcholinesterase (AChE) is primarily responsible for the hydrolysis of ACh and its synaptic clearance (Soreq and Seidman, 2001). Therefore, AChE inhibitors such as rivastigmine can alleviate AD

symptoms by increasing the level of acetylcholine in the synapses and there are several candidate drugs for the clinical management of AD (Anand et al., 2012). On the contrary, anticholinergic drugs, such as scopolamine, can mimic learning and memory impairments associated with AD (Potasiewicz et al., 2020).

In a study carried out by Dastmalchi et al. (2009), the MO extract demonstrated acetylcholinesterase inhibitory activities. Based on their results, the fraction containing rosmarinic acid had the most potent AChE inhibitory effect (Dastmalchi et al., 2009). Another study also confirmed AChE inhibitory effect of rosmarinic acid (Gülçin et al., 2016). Furthermore, AChE inhibitory activity was exhibited by the essential oils from MO (Chaiyana and Okonogi, 2012).

Anti-inflammatory effect of *Melissa officinalis* and memory

Neurodegenerative diseases, including AD, Parkinson's disease and amyotrophic lateral sclerosis (ALS) are often associated with neuroinflammation (Jung et al., 2019; Kitazawa et al., 2005). Synthesis and the release of chemical mediators such as cytokines and chemokines in glial cells, play an important role in neuroinflammation (Kielian, 2004). In animal experiments, lipopolysaccharide (LPS), gram-negative bacteria endotoxin, is used to induce inflammatory responses (Zhao et al., 2019). Intraperitoneal injection of LPS has been shown to induce memory impairments in rodents (Beheshti and Karimi, 2016). Investigation in animal models has

shown that the aqueous extract of MO can inhibit histamine-induced and carrageenan-induced inflammation (Birdane et al., 2007). Additionally, MO essential oil has anti-inflammatory properties (Bounihi et al., 2013). Herbs with anti-inflammatory effects such as MO, might be a potential strategy in the management of inflammatory-induced memory impairments.

Antioxidant effect of *Melissa officinalis* and memory

During oxygen metabolism in the living organisms, reactive oxygen species (ROS) are produced (Liguori et al., 2018). Oxidative stress is imbalanced between ROS and antioxidant defenses, and evidence show that oxidative stress is associated with pathogenesis and progression of AD (Butterfield and Halliwell, 2019) and memory impairments (Alzoubi et al., 2012). It is well established that MO has robust antioxidant activity (Ghazizadeh et al, 2020; Miraj et al., 2017). Moreover, it is shown that the antioxidant activity of MO aqueous extract is related to reducing lipid peroxidation and increasing superoxide dismutase and catalase activities (Martins et al., 2012). Antioxidant properties of MO can be beneficial for the management of oxidative stress associated with memory decline.

Toxicological evaluation of *Melissa officinalis*

The use of traditional and herbal medicines has been increased in the last few years; however, the safety of medicinal plants requires more attention. In other terms, details on the toxicity of the plants are crucial before the development of new herbal medicines. Toxicity of hydro-alcoholic extract of MO was evaluated in an experiment carried out by Hashemnia et al. (2017). Their results showed that chronic (600 and 1200mg/kg for 30 days) oral administration of hydro-alcoholic extract of MO induces hepatic and renal lesions in animals.

Conclusion

MO is a valuable herb that is widely used for therapeutic and non-therapeutic purposes. As mentioned earlier, MO possesses several favorable effects like anti-inflammation, anti-oxidant, AChE inhibition and prevention of beta-amyloid accumulation, and these effects make MO a potential medication for memory enhancement. However,

further studies are required to investigate the safety of long-term consumption of MO. It would be an interesting topic to investigate the AChE inhibitory effect of MO on nicotine addiction treatment.

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Conflict of interest

The authors declared no competing interests.

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