Original Article

Melissa officinalis L: A Review Study With an Antioxidant Prospective

Journal of Evidence-Based Complementary & Alternative Medicine
2017, Vol. 22(3) 385-394

DOI: 10.1177/2156587216663433
journals.sagepub.com/home/cam
SAGE

Sepide Miraj, PhD[1], Rafieian-Kopaei, PhD[1], and Sara Kiani[1]

Abstract

Melissa officinalis is a plant cultivated in some parts of Iran. The leaves of lemon balm, *Melissa officinalis* L (Lamiaceae), are used in Iranian folk medicine for their digestive, carminative, antispasmodic, sedative, analgesic, tonic, and diuretic properties, as well as for functional gastrointestinal disorders. This review article was aimed not only to introduce *Melissa officinalis* (its growth condition, its chemical compounds, and its traditional usages) but also to overview its antioxidant properties in detail. This review was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases up to 2016. The search terms used were "*Melissa officinalis* L," "antioxidant properties," oxidative stress," "oxidative damage", "ROS." Articles whose full texts were not available were excluded from the study. In this study, firstly, traditional usage of this herb was reviewed, including antimicrobial activity (antiparasitic, antibacterial, antiviral, etc), antispasmodic, and insomnia properties. Then, its antioxidant properties were overviewed. Various studies have shown that *Melissa officinalis* L possesses high amount of antioxidant activity through its chemical compounds including high amount of flavonoids, rosmaric acid, gallic acid, phenolic contents. Many studies confirmed the antioxidative effects of *Melissa officinalis*; thus, its effect in preventing and treating oxidative stress-related diseases might be reliable.

Keywords

Melissa officinalis L, traditional usage, antioxidant properties, oxidative stress, oxidative damage, ROS

Received March 11, 2016. Received revised May 22, 2016. Accepted for publication July 16, 2016.

The use of medicinal herbs and herbal medicines is an age-old tradition, and the recent progress in modern therapeutics has stimulated the use of natural products worldwide for diverse ailments and diseases.[1-11] In traditional medicine, folk people used medicinal plants in diverse manners to treat diseases.[12-24] Traditional medicine is popular in all regions of the world, and its use is rapidly expanding even in developed countries.[25-35] For example, in China, traditional herbal preparations account for 30% to 50% of the total medicinal consumption, and now the annual global market for herbal medicine is over US$60 billion. The World Health Organization estimated that over 80% of the people in developing countries rely on traditional remedies such as herbs for their daily needs and about 855 traditional medicines include crude plant extracts. This means that about 3.5 to 4 billion of the global population rely on plants resources for drugs. However, the traditional usages of just some of these medicinal plants have been investigated in vitro and clinical trial studies.[36-44]

In fact, herbal medicines possessing natural essential chemical compounds in their profile could fulfill the primary needs and prerequisite of human beings to cure their diseases.[44-51] It has been reported that natural products, their derivatives and analogs, represent over 50% of all drugs in clinical use, in which natural products derived from higher plants represent about 25% of the total. The diversity of natural compounds in herbs and their different functions in preventing and treating different diseases on the one hand and their property of being natural and comfortable with the body and not having adverse effects providing their proper usage induces people toward their consumption; educated public and health care professionals have enormous interests concentrating studies on these herbs and diagnosing their therapeutic properties, but there is a great deal of confusion about their identification, effectiveness, therapeutic dosage, toxicity, standardization, and regulation.[52-63] To achieve this purpose, lots of studies have been carried out to concentrate on the identification of medicinal herbs triggering economically remarkable chances for farmers and related cultivation, harvesting, and agronomic conditions of the herb to generate

[1] Shahrekord University of Medical Sciences, Shahrekord, Iran

Corresponding Author:
Sara Kiani, Shahrekord University of Medical Sciences, Shahrekord, Iran.
Email: kiani.sandra@yahoo.com

favorable a chemical and pharmacological profile.[64] Economically, cultivating *Melissa officinalis* is cost-effective, and compared with the economic indicators of traditional crops grown on fertilized land, this herb provides much higher profits.[65] This review article is aimed not only to introduce *Melissa officinalis* (its growth condition, its chemical compounds, and its traditional usages) but also to overview its antioxidant properties in detail.

Taxonomy

Melissa officinalis L, also known as lemon balm, bee balm, honey balm,[66] is a perennial herb. It is a member of the Lamiaceae (mint) family, and lemon balm (*Melissa officinalis*) belongs to a genus that includes 5 species of perennial herbs native to Europe, Central Asia, and Iran. Although *Melissa officinalis* originated primarily in Southern Europe, it is now naturalized around the world, from North America to New Zealand.[67] Lemon balm occurs naturally in sandy and scrubby areas[68] but has also been reported to grow on damp wasteland, at elevations ranging from sea level to the mountains. In Iran, this plant is known locally by the names *Badranjbooye*, *Varangboo*, and *Faranjmoshk*.[66]

The taxonomical classification of this plant is as follows: Kingdom: Plantae; Division: Tracheophyta; Subdivision: Speramtophyta; Class: Magnoliopsida; Superorder: Asteranae; Order: Lamiales; Family: Lamiaceae; Genus: *Melissa*; Species: *Melissa officinalis* L.

Cultivation

Lemon balm is probably one of the easiest herbs to grow and is ideal for beginners. This perennial herb grows and spreads so readily that some gardeners consider it a weed.

Traditional Uses

Historically lemon balm has been said to possess sedative/tranquilizing, anti-gas, fever-reducing, antibacterial, spasmolytic,[58] hypotensive, memory-enhancing, menstrual-inducing, and thyroid-related effects; antiviral and antioxidant activities; antifungal, antiparasitic, and antispasmolytic activities; flatulence; asthma; bronchitis; amenorrhea; cardiac failure; arrhythmias; ulcers; and wounds.[59,60] Besides, it has been said that it is effective in treatment of headaches, indigestion, colic, nausea, nervousness, anemia, vertigo, syncope, malaise, insomnia, epilepsy, depression, psychosis, and hysteria.[69]

Chemical Compounds

The leaf of *Melissa officinalis* contains flavonoids (quercitrin, rhamnocitrin, luteolin), polyphenolic compounds (rosmarinic acid, caffeic acid, and protocatechuic acid), monoterpenoid aldehyde, monoterpene glycosides, triterpenes (ursolic and oleanolic acids), sesquiterpenes, tannins, and essential oils (citral).[64] Thirty-three components were identified representing 89.30% of the total oil in the composition of the leaf (Table 1).

Table 1. Chemical Compositions of Melissa Officinalis L.

Main Categories		Diagnosed Organ
Terpenes	α-Pinene	
	cis-p-Meth-2 en-7-ol	
	2-Pinen-4-one	
	Nerol acetate	
	Citronellal, methyl citronellate, citral, citral a (geranial), citral b (neral), ocimene, linalool, and ethric oil	Leaf, oil
	Nerol	
Phenolic compounds	Patchoulene	
	1R-α-Pinene	
	Isogeraniol	
	Geraniol	
	Verbenol	
	Carane	
	Geraniol acetate	
Nitrogen compounds	Menthol	
	Cinerone	
	cis-Z-Bisabolene oxide	
	Verbenone	
	Aromadendrene oxide	
	β-Caryophyllene	Leaf, oil
	β-Caryophyllene oxide	Leaf, oil
	Aromadendrene oxide	
	Andropholide	
	Caryophyllene oxide	
	cis-Myrtanol	
	Germanicol	
	Longifolene	
	Himachalene	
	Himachala-2,4-diene	
	Cubenole	
	Pimara-7,15-dien-3-one	
	Cycloisolengifolene	
	Cholest-5-en-7-ol	
	Lupan-3-ol acetate	
	Eugenylglycoside	Leaf
	Dehydroabietane diterpene hydrocarbon	Leaf

Six predominant components followed in the essential oils from Sefrou lemon balm were citronellal (14.40%), isogeraniol (6.40%), geraniol acetate (10.20%), nerol acetate (5.10%), caryophyllene (8.10%), and caryophyllene oxide (11.00%), representing 55.20% of the total oil (Table 1).[65]

Leaf: Citral, monoterpenes, geranial and neral. Flavonoids such as luteolin-7-o-glucoside (0.0002%)

Oil: Geranial, neral, 6-methyl-5-hepten-2-one, citronellal, geranyl-acetate, β-caryophyllene, and β-caryophyllene-oxide

The dried lemon balm leaves: Citral (neral + geranial) 0.13%, total polyphenol compounds 11.8% comprising total hydroxycinnamic compounds 11.3% (rosmarinic acid 4.1%) and total flavonoid compounds 0.5%.

The lemon balm extract: Hydroxycinnamic acid derivatives and flavonoids with caffeic acid, *m*-coumaric acid, eriodictyol-7-O-glucoside, naringin, hesperidin, rosmarinic acid, naringenin, hesperetin, phenolic content of the extract (gallic acid equivalents).

Pharmacological Activities

Antimicrobial Activity (Antiparasitic, Antibacterial, Antiviral). 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 no significant values of inhibiting activity of M1, M2, and M3 on the same virus in vitro or in vivo were demonstrated. Caffeic, rosmarinic, and ferulic acids contribute to antiviral activity of *Melissa officinalis* L.[68] In a double-blind study, a specially prepared dried extract from *Melissa* leaves was investigated and the antiviral activity in vitro of this plant against herpes simplex infections was confirmed. Besides, the treatment with this plant was shown to be effective at very early stages of the infection.[70] 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 was effective for the treatment of this disease. In addition to the shortening of the healing period, balm mint cream was beneficial in preventing spreading of the infection and contribute to the rapid effect on typical symptoms of herpes like itching, tingling, burning, stabbing, swelling, tautness, and erythema. The different mechanism of action of the balm mint extract rules out the development of resistance of the herpes virus.[69] In an in vitro study, anti-herpes activity of *Melissa officials* was investigated and it was suggested that *Melissa* extract possesses high virucidal activity against herpes simplex virus type 1 (HSV-1), even at very low concentrations of 1.5 μg/mL. Besides, it was indicated that rosmarinic acid mainly contributed to the antiviral activity of *Melissa* extract.[71] 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 nontoxic concentrations of 0.025 to 1 mg mL. This study showed anti-herpes effect of this plant through cinnamic acid–like compounds, mainly rosmarinic acid.[72] In an animal study, the antiviral effect of lemon balm oil on herpes simplex virus (HSV-1 and 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. Considering the lipophilic nature of lemon balm essential oil, which enables it to penetrate the skin, and a high selectivity index, *Melissa officinalis* oil might be suitable for topical treatment of herpetic infections.[69] The effects of the volatile oil components of *Melissa officinalis* was evaluated on HSV-2 replication in HEp-2 cells. Five different concentrations (25, 50, 100, 150, and 200 μg/mL) of volatile oils were examined. The antiviral activity of nontoxic concentrations against HSV-2 was tested. The replication of HSV-2 was inhibited, indicating that the *Melissa officinalis* L extract contains an anti-HSV-2 substance.[69] An aqueous extract of *Melissa officinalis* and the phenolic compounds caffeic acid, p-coumaric acid, and rosmarinic acid were examined for their antiviral activity against HSV-1 acyclovir-sensitive and clinical isolates of acyclovir-resistant strains in vitro. These results indicate that mainly rosmarinic acid contributed to the antiviral activity of *Melissa* extract. Penetration of herpes viruses into cells was inhibited by *Melissa* extract at 80% and 96% for drug-sensitive and drug-resistant viruses, respectively.[69] 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 5 human pathogenic bacteria, 1 yeast *Candida albicans*, and 2 phytopathogenic fungi tested.[72] Antimicrobial activity 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.[69] The antimicrobial properties of essential oil from Romanian *Melissa officinalis* were assayed, which showed a high activity against *Candida albicans*. The gram-negative bacteria were not affected by the lemon balm oil.[69] Antimicrobial activities of the extracts and of rosmarinic acid of this plant were evaluated and were confirmed.[73]

Antispasmodic Activity. The anti-inflammatory activities of *Melissa officinalis* L leaves were investigated. The essential oil of *Melissa officinalis* L was shown to have anti-inflammatory activities, supporting the traditional application of this plant in treating various diseases associated with inflammation and pain.[74] The antinociceptive effect of the ethanolic extract from *Melissa officinalis* L and of the rosmarinic acid in chemical behavioral models of nociception were investigated. The present results suggest that the extract produced dose-related antinociception in several models of chemical pain through muscarinic and nicotinic acetylcholine receptors and the L-arginine-nitric oxide pathway. In addition, the rosmarinic acid contained in this plant appears to contribute to the antinociceptive property of the extract.[69] Efficacy of *Melissa officinalis* in the treatment of infantile colic was evaluated. Eighty-eight infants completed the trial. This study shows that colic in breastfed infant improves within 1 week by treatment with an extract based on *Melissa officinalis*.[69] In an animal study, the relaxant effect of the essential oil of *Melissa officinalis* and its main component, citral, on rat-isolated ileum contractions was evaluated. *Melissa officinalis* essential oil inhibited the response in a concentration-dependent manner. Citral also had a concentration-dependent inhibitory effect.[69]

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.[75] For the first time, it has been shown that chronic administration of *Melissa officinalis* L relieves stress-related effects. It is critical that further studies incorporate a placebo and investigate physiological stress markers.[76]

Antioxidant Activity. The antioxidants are known to play an important role in protection against disorders caused by oxidant damage. Reactive oxygen species (ROS) production can overcome cellular antioxidant defenses and can lead to a condition termed oxidative stress. Of particular importance, oxidative stress has been implicated in the installation and progression of several degenerative diseases, via DNA mutation, protein oxidation, and/or lipid peroxidation. Literature data have given special attention to the role of ROS and oxidative stress in diabetes, cardiovascular diseases, chronic neurodegenerative disorders such as Parkinson's and Alzheimer's diseases, and so on.

It was revealed that essential oils of *Melissa officinalis* L have good potential for antioxidant activity and can be used in lipid-containing foods. It is a rich source of antioxidants, in particular from the group of phenolic compounds.[77] Its activity is comparable with synthetic antioxidants (BHA and BHT), and antioxidant activity is related to phenolic compounds like citronellal and neral.[78]

In a study, water extracts of 6 different herbs of the Lamiaceae family (dittany, lemon balm, mint, sage, siderites, and sweet marjoram) were investigated for their antioxidative properties. The extracts were examined for their effect against lipid oxidation in comparison to a tea water extract. It showed that the extract of *Melissa* was rich in bound forms of phenolic compounds such as hydroxycinnamic acids and flavonoids, rosmarinic and caffeic acids.[79] In another study, essential oil, ethanolic extract, and decoction of 10 plant species from interior Portugal were analyzed for their activity toward acetyl cholinesterase enzyme and their antioxidant activity. *Melissa officinalis* and *Mentha suaveolens* showed acetyl cholinesterase inhibitory capacity is higher than 50% in the essential oil fraction. *Melissa officinalis* showed both high acetyl cholinesterase inhibitory capacity and antioxidant activity. Besides, *Melissa officinalis* showed appreciable antioxidant activity only in the polar fractions.[80] Antioxidant activity of different fractions from *Melissa officinalis* extract was evaluated. Ethyl acetate fraction presented the highest flavonoids content as well as the antioxidant activities when compared with other tested fractions.[81]

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.[82] The ability to scavenge the free radical DPPH (2,2-diphenyl-1-picrylhydrazyl) was very high in lemon balm. It was suggested that *Melissa officinalis* scavenged DPPH radical in a concentration-dependent manner with IC_{50} values of 48.76 $\pm$ 1.94 μg/mL. *Melissa officinalis* showed strong reducing power and exhibited a significant inhibition of deoxyribose degradation.[83] In another study, water extracts of *Melissa officinalis* L suppressed the formation of DPPH, hydroxyl, and lipid peroxyl radicals in a dose-dependent manner. The maximum DPPH and hydroxyl radical scavenging activities were achieved in the presence of *n*-butanol extract at concentrations of 0.4 mg/mL and 0.5 mg/mL, respectively. The highest lipid peroxyl scavenging activity (93.20%) was observed at a higher concentration (5 mg/mL) of *n*-butanol extract in the lipid peroxidation system. The high phenolic content and radical scavenging activities of extracts of *Melissa officinalis* L was confirmed.[84]

In a study, *Melissa officinalis* had very high levels of phenolics (13.2 mg GAE/100 g dw) in 32 plant spices.[85] In another study, it had the highest levels of phenolics and flavonoids.[86]

Four known compounds have been isolated from dried stems and leaves of *Melissa officinalis*. The known compounds were identified as quadranoside III, salvianic acid A, rosmarinic acid, and luteolin. Free radical scavenging and antimicrobial activities of the extracts and of rosmarinic acid, the major component, were evaluated.[87]

The highest value of phenol compounds was obtained for the extracts of solid residues of supercritical extraction at 10 MPa, 323 K, and 30 minutes.[88]

The phenolic profiles of different samples of lemon balm were evaluated. The profiles were compared in order to understand the differences between cultivated, in vitro cultured, and commercial (bags and granulated) samples. Rosmarinic acid was the most abundant compound. Moreover, dimers, trimmers, and tetramers of caffeic acid were identified and quantified for the first time in lemon balm. Only one flavonoid, luteolin-30-O-glucuronide, was found in all the samples. Overall, cultivated and in vitro cultured samples presented the lowest amounts of phenolic compounds; otherwise, commercial samples showed the highest contents.[89]

Antioxidant potential in garden cultivated, in vitro cultured, and 2 commercial samples (bags and granulated) of lemon balm was evaluated and compared. The profile of in vitro cultured lemon balm is closer of garden cultivated sample than of both commercial samples (bag or granulate). Garden cultivated sample presented the highest levels of proteins and ash, and the lowest energetic value. The highest a-linolenic acid, tocopherols (including a-, c-, and d-isoforms), and ascorbic acid contents were also observed in this sample. However, it was the commercial bag lemon balm that gave the highest antioxidant.[90]

In an animal study, *Melissa officinalis* aqueous extract possessed potent antioxidative and neuroprotective properties, validating its efficacy in attenuating Mn-induced oxidative stress in the mouse brain.[91] Some of the individual compounds identified in the samples (mainly rosmarinic acid, which is the most antioxidant agent according to literature) could be responsible for the antioxidant activity of lemon balm.[89]

In another animal study on mice, the antioxidant capacity of *Melissa officinalis* and 2 other plants used in Brazil was

investigated to treat neurological disorders. The antioxidant effect of phenolic compounds commonly found in plant extracts, namely, quercetin, gallic acid, quercitrin, and rutin, was also examined for comparative purposes. *Melissa officinalis* aqueous extract caused the highest decrease in TBARS production induced by all tested pro-oxidants. *Melissa officinalis* presented also the best antioxidant effect, but in this case, the antioxidant potencies were similar for the aqueous, methanolic, and ethanolic extracts. Among the purified compounds, quercetin had the highest antioxidant activity followed by gallic acid, quercitrin, and rutin.[92] It was indicated that *Melissa officinalis* could be considered an effective agent in the prevention of various neurological diseases associated with oxidative stress in mice.[69]

In a clinical trial the capability of *Melissa officinalis* L infusion on improvement of oxidative stress status was studied in radiology staff. It was concluded that infusion of lemon balm markedly improve oxidative stress condition and DNA damage in radiology staff when used as a dietary supplement for radiation protection.[93]

In another animal study on boars, the protective ability of extracts of mate tea and lemon balm was investigated. It was indicated that the highest concentration of lemon balm produced significant improvement in curvilinear trajectory, straightness, and amplitude of lateral head displacement after thawing.[94]

Mechanisms of Action

Antioxidants act in one or more of the following ways: reducing agents, free radical scavengers, potential complexes of prooxidant metals, and quenchers of singlet oxygen.[95-97]

Lemon balm has shown to possess high phenolic content and antioxidant properties. Antioxidant activity of lemon balm has been shown as evidenced by the reduction of DPPH. Also, studies have demonstrated that the cytoprotective effect of lemon balm extracts seen in rats was partly due to free radical scavenging properties.[95,96] Besides, it could protect against oxidative damage induced by various pro-oxidant agents that induce lipid peroxidation by different processes. Thus, plant extracts could inhibit the generation of early chemical reactive species that subsequently initiate lipid peroxidation or, alternatively, they could block a common final pathway in the process of polyunsaturated fatty acids peroxidation. Lemon balm infusion improves plasma levels of catalase, superoxide dismutase, and glutathione peroxidase and a marked reduction in plasma DNA damage, myeloperoxidase, and lipid peroxidation. Due to its iron(II) chelating activity of the extract, its antioxidant potential was increased.[82] It was found that flavonoids aglycones were responsible for the free radical scavenging activity and that induced lipid peroxidation in rat cultured hippocampal neurons was significantly inhibited by fractions containing flavonol glycosides, flavonol and biflavone aglycones, or chlorogenic acid type phenolics present in the ethanolic extract.[80]

Phenolic compounds are the most important compounds that have antioxidant activities.[59,97-107]

To balance the oxidative state, plants and animals maintain complex systems of overlapping antioxidants, such as glutathione and enzymes (eg, catalase and superoxide dismutase) produced internally or vitamin C, vitamin A, and vitamin E obtained by ingestion.

Antioxidants are widely used in dietary supplements and have been investigated for the prevention of diseases such as cancer or coronary heart disease. The hypothesis that antioxidant supplements might promote health has not been confirmed experimentally. Trials including β-carotene, vitamin A, and vitamin E singly or in different combinations have indicated that supplementation has no effect on mortality or might increase it.[64,65] Randomized clinical trials of taking antioxidants including β-carotene, vitamin E, vitamin C, and selenium have shown no effect on cancer risk or have increased cancer risk.[47,52] Supplementation with selenium or vitamin E does not reduce the risk of cardiovascular disease.[81,82]

Antioxidants have many industrial uses, such as preservatives in food and cosmetics and to prevent the degradation of rubber and gasoline.[81]

Discussion

In this study, first traditional usages of *Melissa officinalis* and second its antioxidant properties were reviewed in detail. The findings of this study indicated that the antioxidant activity of this plant was mainly attributed to the phenolic compounds of the plant, either in plants of different origin or prepared by differing extraction methods.

The phytochemical analysis of *Melissa officinalis* has revealed a large number of compounds including high amount of flavonoids, rosmaric acid, gallic acid, phenolic contents, and so on, which have been shown to have potent antioxidant properties[64,65] acting in a synergistic way. It was found that the antioxidant activity of phenolic compounds in the plant extract is mostly because of rutin, quercitrin, galic acid, and quercetin, with the highest antioxidant activity belonging to quercetin and then to galic acid, quercitrin, and rutin, respectively. The extract of this plant is able to prevent the production of chemically active species and it may block lipid peroxidation through various processes.[108]

Evidence from numerous clinical and experimental studies has shown the significant protective effects of phenolic compounds against oxidative damage in disease treatment and prevention. For example, it was shown in a study that *Melissa officinalis* extract could prevent neurological diseases associated with oxidative stress.[69]

In addition, it was shown that the antioxidant activities of similar phenolic-containing compounds are not identical, suggesting that each compound must be examined individually for its antioxidant behavior.[69]

A positive and significant correlation existed between antioxidant activity and total phenolic content, revealing that phenolic compounds were the dominant antioxidant components in this plant. It was revealed that essential oils of *Melissa officinalis* L have good potential for antioxidant activity and can be

used in lipid containing foods. It is rich sources of antioxidants, in particular, from the group of phenolic compounds like citronellal and neral.[77] *Melissa officinalis* had very high levels of phenolics (13.2 mg GAE/100 g dw) in 32 plant spices.[85] Besides, it was suggested that it had the highest levels of phenolics and flavonoids.[86] The highest value of its phenol compounds was obtained for the extracts of solid residues of supercritical extraction at 10 MPa, 323 K, and 30 minutes.[88]

The extract of the plant can have a significant role in maintaining health and curing diseases because of its volatile organic compounds and its active constituents such as terpenoids, flavonoids, quercetin, rutin, quercitrin, gallic acid, and high antioxidant capacity. Essential oil of *Melissa officinalis* showed both high acetyl cholinesterase inhibitory capacity and antioxidant activity. Besides, *Melissa officinalis* showed remarkable antioxidant activity only in the polar fractions.[80] Rosmarinic acid was the most abundant compound in this plant.[89]

Comparison of cultivated and in vitro cultured and commercial samples of *Melissa* in the DPPH assay showed the lowest amounts of phenolic compounds for the 2 first and the highest contents for the commercial samples.[90]

Finally, several studies of very different quality reported a radical scavenging and antioxidant potential of polar extracts from *Melissa*. These activities have arisen from the content of flavonoids, rosmarinic acid, and the benzodioxole.[80] The antioxidant effects of these compounds are up to 10 times stronger than the effects of those of vitamins B and C.[64]

Gaps of Study

Results of this study showed that most investigations on the therapeutic activities of this plant have been carried out in in vitro studies. Thus, more complementary studies in different therapeutic effects of this plant are required in clinical trial studies. Despite the studies on antioxidant activities, more profound research on the toxicity and its teratogenicity should be done. Besides, although there are different genus of this plant that each one has its own chemical compounds, most of them have common chemical compounds that trigger their antioxidant properties. Thus, more studies are needed to diagnose new chemical compounds in a safe dose on the untested genus of this plant causing its antioxidant activity.

Conclusion and Further Suggestions

In this study, first traditional usages of *Melissa officinalis* and second its antioxidant properties were reviewed in detail. Regarding its traditional usage, antimicrobial activity (antiparasitic, antibacterial, antiviral, etc), antispasmodic, insomnia properties were reported. Many studies confirmed the antioxidative effects of *Melissa officinalis*; thus, its effect in preventing and treating oxidative stress-related diseases might be reliable. The results of numerous studies on antioxidant or radical scavenging effects may be a basis for detailed in vivo research on anti-inflammatory activities of this plant.

Further studies are needed to conduct clinical trials on cancer to develop new anticancer drugs. Future research should be focused on the relationship between the total antioxidant capacity and the content, as well as composition of antioxidants. Further studies are also required to study the mechanism of antioxidant activity of phenolic compounds. Such studies would provide a greater understanding of how ROS scavenging and metal-binding antioxidant mechanisms afford oxidative protection as well as facilitate improved antioxidant design for the treatment and prevention of disease. We should also investigate the interrelationship between phenolic compounds and antioxidant/anticancer activity to illustrate possible mechanisms for cancer prevention and treatment.

Side Effects

No side effects have so far been reported for the herb[98] 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

It was reported to be unsafe during pregnancy or lactation or in pediatric patients, and when used in patients with thyroid disorders or in combination with sedatives.[109]

Acknowledgments

The authors thank all those who cooperated with us both financially and technically.

Author Contributions

SM, SK: concept and design, supervision. MRK, SK, MAS: data collection, manuscript drafting.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Shahrekord University of Medical Sciences.

Ethical Approval

As no human subjects were involved, this study did not require ethical approval.

References

1. Bahmani M, Farkhondeh T, Sadighara P. The anti-parasitic effects of *Nicotina tabacum* on leeches. *Comp Clin Pathol*. 2012;21:357-359.

2. Bahmani M, Karamati SA, Banihabib EKH, Saki K. Comparison of effect of nicotine and levamisole and ivermectin on mortality of leech. *Asian Pac J Trop Dis*. 2014;4(suppl 1):477-480.
3. Bahmani M, Banihabib EKH. Comparative assessment of the anti-*Annelida* (Limnatisnilotica) activity of nicotine with niclosamide. *Global Vet*. 2013;10:153-157.
4. Amirmohammadi M, Khajoenia SH, Bahmani M, Rafieian-Kopaei M, Effekhari Z, Qorbani M. In vivo evaluation of antiparasitic effects of *Artemisia abrotanum* and *Salvia officinalis* extracts on *Syphacia obvelata*, *Aspiculoris tetrapetra* and *Hymenolepis nana* parasites. *Asian Pac J Trop Dis*. 2014;4(suppl 1):250-254.
5. Eftekhari Z, Bahmani M, Mohsenzadegan A, Ahangaran MG, Abbasi J, Alighazi N. Evaluating the anti-leech (*Limnatis nilotica*) activity of methanolic extract of *Allium sativum* L. compared with levamisole and metronidazole. *Comp Clin Path*. 2012;21: 1219-1222.
6. Bahmani M, Abbasi J, Mohsenzadegan A, Sadeghian S, Ahangaran MG. *Allium sativum* L.: the anti-immature leech (*Limnatis nilotica*) activity compared to Niclosomide. *Comp Clin Pathol*. 2013;22:165-168.
7. Gholami-Ahangaran M, Bahmani M, Zia-Jahromi N. Comparative and evaluation of anti-leech (*Limnatis nilotica*) effect of olive (*Olea europaea* L.) with levamisol and tiabendazole. *Asian Pac J Trop Dis*. 2012;2:S101-S103.
8. Bahmani M, Golshahi H, Mohsenzadegan A, Ahangarani MG, Ghasemi E. Comparative assessment of the anti-*Limnatis nilotica* activities of *Zingiber officinale* methanolic extract with levamisole. *Comp Clin Path*. 2013;22:667-670.
9. Esteki R, Miraj S. The abortificient effects of hydroalcoholic extract of lawsonia inermis on BALB/c mice. *Electron Physician*. 2016;8(6):2568-2575.
10. Baghbahadorani FK, Miraj S. The impact of Silymarin on improvement of platelet abnormalities in patients with severe preeclampsia. *Electron Physician*. 2016;8(5):2436-2442.
11. Masoudi M, Miraj S, Rafieian-Kopaei M. Comparison of the effects of Myrtus communis L, berberis vulgaris and metronidazole vaginal gel alone for the treatment of bacterial vaginosis. *J Clin Diagn Res*. 2016;10(3):Qc04-7.
12. Seyyedi F, Rafiean-Kopaei M, Miraj S. Comparison of the effects of vaginal royal jelly and vaginal estrogen on quality of life, sexual and urinary function in postmenopausal women. *J Clin Diagn Res*. 2016;10(5):Qc01-5.
13. Masoudi M, Miraj S. A comparison of the efficacy of metronidazole vaginal gel and Myrtus (Myrtus communis) extract combination and metronidazole vaginal gel alone in the treatment of recurrent bacterial vaginosis. *Avicenna J Phytomed*. 2016:1-7.
14. Davar R, Miraj S, Mojtahedi MF. Effect of adding human chorionic gonadotropin to frozen thawed embryo transfer cycles with history of thin endometrium. *Int J Reprod Biomed*. 2016;14(1):53.
15. Davar R, Mojtahedi MF, Miraj S. Effects of single dose GnRH agonist as luteal support on pregnancy outcome in frozen-thawed embryo transfer cycles: an RCT. *Iran J Reprod Med*. 2015;13(8): 483.
16. Eftekhar M, Miraj S, Mortazavifar Z. The effect of luteal phase gonadotropin-releasing hormone antagonist administration on IVF outcomes in women at risk of OHSS. *Int J Reprod Biomed*. 2016;14(8):507-510.
17. Karamati SA, Hassanzadazar H, Bahmani M, Rafieian-Kopaei M. Herbal and chemical drugs effective on malaria. *Asian Pac J Trop Dis*. 2014;4(suppl 2):599-601.
18. Bahmani M, Karamati SA, Hassanzadazar H, et al. Ethnobotanic study of medicinal plants in Urmia city: identification and traditional using of antiparasites plants. *Asian Pac J Trop Dis*. 2014; 4(suppl 2):906-910.
19. Ebrahimie M, Bahmani M, Shirzad H, Rafieian-Kopaei M, Saki K. A review study on the effect of Iranian herbal medicines on opioid withdrawal syndrome. *J Evid Based Complementary Altern Med*. 2015;20:302-309.
20. Delfan B, Bahmani M, Rafieian-Kopaei M, Delfan M, Saki K. A review study on ethnobotanical study of medicinal plants used in relief of toothache in Lorestan Province, Iran. *Asian Pac J Trop Dis*. 2014;4(suppl 2):879-884.
21. Delfan B, Bahmani M, Hassanzadazar H, Saki K, Rafieian-Kopaei M. Identification of medicinal plants affecting on headaches and migraines in Lorestan Province, West of Iran. *Asian Pac J Trop Med*. 2014;7(suppl 1):376-379.
22. Saki K, Bahmani M, Rafieian-Kopaei M. The effect of most important medicinal plants on two important psychiatric disorders (anxiety and depression)—a review. *Asian Pac J Trop Med*. 2014; 7(suppl 1):34-42.
23. Saki K, Bahmani M, Rafieian-Kopaei M, et al. The most common native medicinal plants used for psychiatric and neurological disorders in Urmia city, northwest of Iran. *Asian Pac J Trop Dis*. 2014;4(suppl 2):895-901.
24. Sarrafchi A, Bahmani M, Shirzad H, Rafieian-Kopaei M. Oxidative stress and Parkinson's disease: new hopes in treatment with herbal antioxidants. *Curr Pharm Des*. 2015;22:238-246.
25. Bahmani M, Zargaran A, Rafieian-Kopaei M, Saki M. Ethnobotanical study of medicinal plants used in the management of diabetes mellitus in the Urmia, Northwest Iran. *Asian Pac J Trop Med*. 2014;7(suppl 1):348-354.
26. Asadbeigi M, Mohammadi T, Rafieian-Kopaei M, Saki K, Bahmani M, Delfan M. Traditional effects of medicinal plants in the treatment of respiratory diseases and disorders: an ethnobotanical study in the Urmia. *Asian Pac J Trop Med*. 2014; 7(suppl 1):S364-S368.
27. Bahmani M, Tajeddini P, Ezatpour B, Rafieian-Kopaei M, Naghdi N, Asadi-Samani M. Ethenobothanical study of medicinal plants against parasites detected in Shiraz, southern part of Iran. *Der Pharmacia Lettre*. 2016;8(1):153-160.
28. Asadi-Samani M, Kafash-Farkhad N, Azimi N, Fasihi A, Alinia-Ahandani E, Rafieian-Kopaei M. Medicinal plants with hepatoprotective activity in Iranian folk medicine. *Asian Pac J Trop Biomed*. 2015;5:146-157.
29. Delfan B, Bahmani M, Eftekhari Z, et al. Effective herbs on the wound and skin disorders: a ethnobotanical study in Lorestan province, west of Iran. *Asian Pac J Trop Dis*. 2014;4(suppl 2):938-942.
30. Baharvand-Ahmadi B, Bahmani M, Naghdi N, Saki K, Baharvand-Ahmadi S, Rafieian-Kopaei M. Medicinal plants used to treat infectious and non-infectious diseases of skin and skin

appendages in city of Urmia, northwest Iran. *Der Pharmacia Lettre*. 2015;7(11):189-196.
31. Bahmani M, Mirhoseini M, Shirzad H, Sedighi M, Shahinfard N, Rafieian-Kopaei M. A review on promising natural agents effective on hyperlipidemia. *J Evid Based Complementary Altern Med*. 2015;20:228-238.
32. Bahmani M, Eftekhari Z, Saki K, Fazeli-Moghadam E, Jelodari M, Rafieian-Kopaei M. Obesity phytotherapy: review of native herbs used in traditional medicine for obesity. *J Evid Based Complementary Altern Med*. 2016;21:228-234.
33. Bahmani M, Sarrafchi A, Shirzad H, Rafieian-Kopaei M. Autism: pathophysiology and promising herbal remedies. *Curr Pharm Des*. 2015;22:277-285.
34. Asadi-Samani M, Rafieian-Kopaei M, Azimi N. Gundelia: a systematic review of medicinal and molecular perspective. *Pak J Biol Sci*. 2013;16:1238-1247.
35. Baharvand-Ahmadi B, Bahmani M, Zargaran A, et al. *Ruta graveolens* plant: a plant with a range of high therapeutic effect called cardiac plant. *Der Pharmacia Lettre*. 2015;7(11):172-173.
36. Bahmani M, Eftekhari Z. An ethnoveterinary study of medicinal plants in treatment of diseases and syndromes of herd dog in southern regions of Ilam province, Iran. *Comp Clin Path*. 2012;22:403-407.
37. Asadi-Samani M, Bahmani M, Rafieian-Kopaei M. The chemical composition, botanical characteristic and biological activities of *Borago officinalis*: a review. *Asian Pac J Trop Med*. 2014;7(suppl 1):22-28.
38. Bahmani M, Rafieian-Kopaei M, Jeloudari M, et al. A review of the health effects and uses of drugs of plant licorice (*Glycyrrhiza glabra* L.) in Iran. *Asian Pac J Trop Dis*. 2014;4(suppl 2):847-849.
39. Bahmani M, Rafieian M, Baradaran A, Rafieian S, Rafieian-Kopaei M. Nephrotoxicity and hepatotoxicity evaluation of *Crocus sativus* stigmas in neonates of nursing mice. *J Nephropathol*. 2014;3(2):81-85.
40. Kooti W, Ghasemiboroon M, Ahangarpoor A, Zamani M. The effect of hydro-alcoholic extract of celery on male rats in fertility control and sex ratio of rat offspring. *J Babol Univ Med Sci*. 2014; 16(4):43-49.
41. Kooti W, Ghasemiboroon M, Asadi-Samani M, et al. The effect of halcoholic extract of celery leaves on the delivery rate (fertilization and stillbirths), the number, weight and sex ratio of rat off spring. *Adv Environ Biol*. 2014;8:824-830.
42. Shayganni E, Bahmani M, Asgary S, Rafieian-Kopaei M. Inflammaging and cardiovascular disease: management by medicinal plants [published online December 3, 2015]. *Phytomedicine*. doi:10.1016/j.phymed.2015.11.004.
43. Bahmani M, Shirzad H, Mirhosseini M, Mesripour A, Rafieian-Kopaei M. A review on ethnobotanical and therapeutic uses of fenugreek (*Trigonella foenum-graceum* L). *J Evid Based Complementary Altern Med*. 2016;21:53-62.
44. Baharvand-Ahmadi B, Bahmani M, Naghdi N, Saki K, Baharvand-Ahmadi S, Rafieian-Kopaei M. Review on phytochemistry, therapeutic and pharmacological effects of myrtus (*Myrtus communis*). *Der Pharmacia Lettre*. 2015;7(11):160-165.
45. Shaygannia E, Bahmani M, Zamanzad B, Rafieian-Kopaei M. A review study on *Punica granatum* L. *J Evid Based Complementary Altern Med*. 2016;21:221-227.
46. Ghasemi Pirbalouti A, Momeni M, Bahmani M. Ethnobotanical study of medicinal plants used by Kurd tribe in Dehloran and Abdanan Districts, Ilam Province, Iran. *Afr J Tradit Complement Altern Med*. 2013;10:368-385.
47. Asadi-Samani M, Kooti W, Aslani E, Shirzad H. A systematic review of Iran's medicinal plants with anticancer effects. *J Evid Based Complementary Altern Med*. 2016;21:143-153.
48. Beyrami-Miavagi A, Farokhi F, Asadi-Samani M. A study of the effect of prostodin and hydroalcoholic extract of *Malva neglecta* on kidney histopathology and renal factors in female rats. *Adv Environ Biol*. 2014;8:942-947.
49. Kooti W, Ahangarpoor A, Ghasemiboroon M, et al. Effect of *Apium graveolens* leaf extract on serum level of thyroid hormones in male rat. *J Babol Univ Med Sci*. 2014;16(11):44-50.
50. Bahmani M, Zargaran A, Rafieian-Kopaei M. Identification of medicinal plants of Urmia for treatment of gastrointestinal disorders. *Rev Bras Farmacogn*. 2014;24:468-480.
51. Bahmani M, Shirzad HA, Majlesi M, Shahinfard N, Rafieian-Kopaei M. A review study on analgesic applications of Iranian medicinal plants. *Asian Pac J Trop Med*. 2014;7(suppl 1): 43-53.
52. Azadmehr A, Hajiaghaee R, Afshari A, et al. Evaluation of in vivo immune response activity and in vitro anti-cancer effect by *Scrophularia megalantha*. *J Med Plants Res*. 2011;5:2365-2368.
53. Rabiei Z, Bigdeli MR, Asadi-Saamni M. The effect of dietary virgin olive oil on brain lipid levels and brain edema in rat stroke models. *ZUMS J*. 2013;21(86):56-64.
54. Kooti W, Ghasemiboroon M, Asadi-Samani M, Gerdabi ND. The effects of hydro-alcoholic extract of celery on lipid profile of rats fed a high fat diet. *Adv Environ Biol*. 2014;8:325-330.
55. Mardani S, Nasri H, Hajian S, Ahmadi A, Kazemi R, Rafieian-Kopaei M. Impact of *Momordica charantia* extract on kidney function and structure in mice. *J Nephropathol*. 2014;3(1):35-40.
56. Nasri H, Ahmadi A, Baradaran A, et al. Clinicopathological correlations in lupus nephritis; a single center experience. *J Nephropathol*. 2014;3:115-120.
57. Nasri H, Rafieian-Kopaei M. Tubular kidney protection by antioxidants. *Iran J Public Health*. 2013;42:1194-1196.
58. Nasri H, Rafieian-Kopaei M. Oxidative stress and aging prevention. *Int J Prev Med*. 2013;4:1101-1102.
59. Setorki M, Rafieian-Kopaei M, Merikhi A, et al. Suppressive impact of *Anethum graveolens* consumption on biochemical risk factors of atherosclerosis in hypercholesterolemic rabbits. *Int J Prev Med*. 2013;4:889-895.
60. Akhlaghi M, Shabanian G, Rafieian-Kopaei M, Parvin N, Saadat M, Akhlaghi M. *Citrus aurantium* blossom and preoperative anxiety. *Rev Bras Anestesiol*. 2011;61:702-712.
61. Rabiei Z, Rafieian-Kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of *Zizyphus jujube* extract on memory and learning impairment induced by bilateral electric lesions of the nucleus Basalis of Meynert in rat. *Neurochem Res*. 2014;39:353-360.
62. Mirhosseini M, Baradaran A, Rafieian-Kopaei M. *Anethum graveolens* and hyperlipidemia: a randomized clinical trial. *J Res Med Sci*. 2014;19:758-761.
63. Rafieian-Kopaei M, Shahinfard N, Rouhi-Boroujeni H, Gharipour M, Darvishzadeh-Boroujeni P. Effects of *Ferulago angulata*

extract on serum lipids and lipid peroxidation. *Evid Based Complement Alternat Med*. 2014;2014:680856.
64. Sofowora A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. *Afr J Tradit Complement Altern Med*. 2013;10:210-229.
65. Gurčík Ľ, Dúbravská R, Miklovičová J. Economics of the cultivation of *Salvia officinalis* and Melissa officinalis. *Agric Econ Czech*. 2005;51:348-356.
66. Rasmussen P. Lemon balm—*Melissa officinalis*, also known as lemon balm, bee balm, garden balm, Melissa, melissengeist. *J Prim Health Care*. 2011;3:165-166.
67. Jastrzębska-Stojko Z, Stojko R, Rzepecka-Stojko A, Kabała-Dzik A, Stojko J. Biological activity of propolis-honey balm in the treatment of experimentally-evoked burn wounds. *Molecules*. 2013;18:14397-14413.
68. Schnitzler P, Schuhmacher A, Astani A, Reichling J. *Melissa officinalis* oil affects infectivity of enveloped herpesviruses. *Phytomedicine*. 2008;15:734-740.
69. Wolbling RH, Leonhardt K. Local therapy of herpes simplex with dried extract from *Melissa officinalis*. *Phytomedicine*. 1994;1(1):25-31.
70. Dimitrova Z, Dimov B, Manolova N, Pancheva S, Ilieva D, Shishkov S. Antiherpes effect of *Melissa officinalis* L. extracts. *Acta Microbiol Bulg*. 1993;29:65-72.
71. Astani A, Reichling J, Schnitzler P. *Melissa officinalis* extract inhibits attachment of herpes simplex virus in vitro. *Chemotherapy*. 2012;58:70-77.
72. Mazzanti G, Battinelli L, Pompeo C, et al. Inhibitory activity of *Melissa officinalis* L. extract on herpes simplex virus type 2 replication. *Nat Prod Res*. 2008;22:1433-1440.
73. Abdellatif F, Boudjella H, Zitouni A, Hassani A. Chemical composition and antimicrobial activity of the essential oil from leaves of Algerian *Melissa officinalis* L. *EXCLI J*. 2014;13: 772-781.
74. Bounihi A, Hajjaj G, Alnamer R, Cherrah Y, Zellou A. In vivo potential anti-inflammatory activity of *Melissa officinalis* L. essential oil. *Adv Pharmacol Sci*. 2013;2013:101759.
75. Müller SF, Klement S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. *Phytomedicine*. 2006;13:383-387.
76. Cases J, Ibarra A, Feuillere N, Roller M, Sukkar SG. Pilot trial of *Melissa officinalis* L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. *Med J Nutr Metab*. 2011;4: 211-218.
77. Capecka E, Mareczek A, Leja M. Antioxidant activity of fresh and dry herbs of some Lamiaceae species. *Food Chem*. 2005;93: 223-226.
78. Meftahizade H, Sargsyan E, Moradkhani H. Investigation of antioxidant capacity of *Melissa officinalis* L. essential oils. *J Med Plant Res*. 2010;4:1391-1395.
79. Triantaphyllou K, Blekas G, Boskou D. Antioxidative properties of water extracts obtained from herbs of the species Lamiaceae. *Int J Food Sci Nutr*. 2001;52:313-317.
80. Ferreira A, Proenca C, Serralheiro M, Araujo M. The in vitro screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from Portugal. *J Ethnopharmacol*. 2006;108:31-37.
81. Pereira RP, Boligon AA, Appel AS, et al. Chemical composition, antioxidant and anticholinesterase activity of *Melissa officinalis*. *Industrial Crops Products*. 2014;53:34-45.
82. Dastmalchi K, Dorman HD, Oinonen PP, Darwis Y, Laakso I, Hitunen R. Chemical composition and in vitro antioxidative activity of a lemon balm (*Melissa officinalis* L.) extract. *LWT Food Sci Technol*. 2008;41:391-400.
83. Kamdem JP, Adeniran A, Boligon AA, Athyade ML. Antioxidant activity, genotoxicity and cytotoxicity evaluation of lemon balm (*Melissa officinalis* L.) ethanolic extract: its potential role in neuroprotection. *Industrial Crops Products*. 2013;51:26-34.
84. Canadanovic-Brunet J, Cetkovic G, Djilas S, et al. Radical scavenging, antibacterial, and antiproliferative activities of *Melissa officinalis* L. extracts. *J Med Food*. 2008;11:133-143.
85. Wojdyło A, Oszmiański J, Czemerys R. Antioxidant activity and phenolic compounds in 32 selected herbs. *Food Chem*. 2007;105: 940-949.
86. Dias MI, Barros L, Sousa MJ, Ferreira IC. Systematic comparison of nutraceuticals and antioxidant potential of cultivated, in vitro cultured and commercial *Melissa officinalis* samples. *Food Chem Toxicol*. 2012;50:1866-1873.
87. Mencherini T, Picerno P, Scesa C, Aquino R. Triterpene, antioxidant, and antimicrobial compounds from *Melissa officinalis*. *J Nat Prod*. 2007;70:1889-1894.
88. Ribeiro M, Bernardo-Gil M, Esquıvel M. *Melissa officinalis* L.: study of antioxidant activity in supercritical residues. *J Supercritical Fluids*. 2001;21:51-60.
89. Barros L, Dueñas M, Dias MI, Sousa MJ, Santos-Buelga C, Ferreira IC. Phenolic profiles of cultivated, in vitro cultured and commercial samples of *Melissa officinalis* L. infusions. *Food Chem*. 2013;136:1-8.
90. Herodež ŠS, Hadolin M, Škerget M, Knez Ž. Solvent extraction study of antioxidants from Balm (*Melissa officinalis* L.) leaves. *Food Chem*. 2003;80:275-282.
91. Martins EN, Pessano NT, Leal L, et al. Protective effect of *Melissa officinalis* aqueous extract against Mn-induced oxidative stress in chronically exposed mice. *Brain Res Bull*. 2012;87:74-79.
92. Pereira RP, Fachinetto R, de Souza Prestes A, et al. Antioxidant effects of different extracts from *Melissa officinalis*, *Matricaria recutita* and *Cymbopogon citratus*. *Neurochem Res*. 2009;34: 973-983.
93. Zeraatpishe A, Oryan S, Bagheri MH, et al. Effects of *Melissa officinalis* L. on oxidative status and DNA damage in subjects exposed to long-term low-dose ionizing radiation. *Toxicol Ind Health*. 2011;27:205-212.
94. Luño V, Gil L, Olaciregui M, Jerez RA, de Blas I, Hozbor F. Antioxidant effect of lemon balm (*Melissa officinalis*) and mate tea (*Ilex paraguensys*) on quality, lipid peroxidation and DNA oxidation of cryopreserved boar epididymal spermatozoa. *Andrologia*. 2015;47:1004-1011.
95. Lamaison J, Petitjean-Freytet C, Carnat A. Medicinal Lamiaceae with antioxidant properties, a potential source of rosmarinic acid [in French]. *Pharm Acta Helv*. 1990;66(7):185-188.

96. Khayyal MT, El-Ghazaly MA, Kenawy SA, et al. Antiulcerogenic effect of some gastrointestinally acting plant extracts and their combination. *Arzneimittelforschung*. 2000;51:545-553.
97. Madihi Y, Merrikhi A, Baradaran A, et al. Impact of Sumac on postprandial high-fat oxidative stress. *Pak J Med Sci*. 2013;29: 340-345.
98. Rafieian-Kopaie M, Baradaran A. Plants antioxidants: from laboratory to clinic. *J Nephropathol*. 2013;2:152-153.
99. Nasri H, Rafieian-Kopaei M. Medicinal plants and antioxidants: why they are not always beneficial? *Iran J Public Health*. 2014; 43:255-257.
100. Rafieian-Kopaei M, Baradaran A, Rafieian M. Oxidative stress and the paradoxical effects of antioxidants. *J Res Med Sci*. 2013;18:628.
101. Nasri H, Rafieian-Kopaei M. Protective effects of herbal antioxidants on diabetic kidney disease. *J Res Med Sci*. 2014;19:82-83.
102. Baradaran A, Nasri H, Nematbakhsh M, Rafieian-Kopaei M. Antioxidant activity and preventive effect of aqueous leaf extract of Aloe Vera on gentamicin-induced nephrotoxicity in male Wistar rats. *Clin Ter*. 2014;165:7-11.
103. Nasri H, Tavakoli M, Ahmadi A, Baradaran A, Nematbakhsh M, Rafieian-Kopaei M. Ameliorative effect of melatonin against contrast media induced renal tubular cell injury. *Pak J Med Sci*. 2014;30:261-265.
104. Rafieian-Kopaei M, Nasri H. Re: Erythropoietin ameliorates oxidative stress and tissue injury following renal ischemia/ reperfusion in rat kidney and lung. *Med Princ Pract*. 2014; 23:95.
105. Baradaran A, Nasri H, Rafieian-Kopaei M. Comment on: Antioxidative stress activity of *Stachys lavandulifolia* aqueous extract in humans. *Cell J*. 2013;15:272-273.
106. Sedighi M, Nasri H, Rafieian-kopaei M, Mortazaei S. Reversal effect of *Achillea millefolium* extract on ileum contractions. *J Herb Med Pharmacol*. 2013;2(1):5-8.
107. Shirzad H, Taji F, Rafieian-Kopaei M. Correlation between antioxidant activity of garlic extracts and WEHI-164 fibrosarcoma tumor growth in BALB/c mice. *J Med Food*. 2011; 14:969-974.
108. Zarei A, Changizi-Ashtiyani S, Taheri S, Hosseini N. A brief overview of the effects of *Melissa officinalis* L. extract on the function of various body organs. *Zahedan J Res Med Sci*. 2015;17(7). http://www.zjrms.ir/files/site1/user_files_10e1c1/ashtiyani-A-10-898-8-6b016f7.pdf. Accessed July 29, 2016.
109. Ulbricht C, Brendler T, Gruenwald J, et al. Lemon balm (*Melissa officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother*. 2004;5(4):71-114.