**Pharmaceuticals and Therapeutic Potentialities of *Melissa officinalis* L. –**

A Review

# ABSTRACT

*Melissa officinalis* is used for its therapeutic properties all over the world in the prevention of numerous diseases. It has several bioactive compounds viz. flavonoids, terpenoids, phenolic acids, tannins, and essential oil. Triterpenes (ursolic acid and oleanolic acid), phenolic acids (rosmarinic acid, caffeic acid, and chlorogenic acid), flavonoids (quercetin, rhamnocitrin, and luteolin), and volatile chemicals (geranial, neral, citronellal, and geraniol) etc*.* The biological researches indicate that *Melissa officinalis* essential oil and extracts include active components that determine a variety of pharmacological actions with potential medical applications*.* This review sought to summarize *Melissa officinal's* botanical traits, traditional uses, phytochemicals, and its pharmacological actions

which indicate the effective use of *Melissa officinalis* as an alternate treatment option for combating numerous disorders due to the presence of vast amount of phytochemical constituents contributing to its various therapeutic potential.

*Keywords: Melissa officinalis; phytochemicals; therapeutic uses; vasorelaxant; analgesic; hypnotic.*

# INTRODUCTION

The use of nutritional plants and herbal preparations as alternatives to medications has attracted substantial attention worldwide. For many disorders that may be cured, traditional medications were utilized by 80% of the population in developing nations (Miraj et al., 2017). The use of medicinal plants in clinical research and investigations has lately increased due to their lower risk of side effects and accessibility (Dragičić et al., 2021). Based onthat experience, employing natural treatments can be a significant method for reducing cardio-metabolic problems.

*Melissa officinalis* (MO), also called lemon balm, is a perennial herbaceous plant that consists of a variety of potent phytochemicals, including flavanols, phenolic acids, and triterpenes.MO belongs to the plant family Lamiaceae (mint), which includes the genus *Melissa L*. (Shakeri et al., 2016). Though native to southern Europe, Central Asia, and western Asia, especially the region of the Mediterranean*, M. officinalis* was indigenous to numerous regions of US (United States), including the Midwestern, Eastern, and Pacific North-west states (Abdel-Naime et al., 2016). Although lemon balm has been observed to flourish on moist wastelands at altitudes from sea level to mountains, it naturally grows over

sandy and scrubby environments (Rasmussen, 2011).

Since ancient times, *Melissa officinalis* (MO) has been used as a traditional medicine in Asia for treating various ailments, including rheumatism, gastrointestinal issues, and neurological diseases (Emamghoreishi & Talebianpour, 2015; Moradkhani et al., 2010). Due to its pleasant odor, MO is commonly used in aromatherapy and the food industry. Extracts of *Melissa officinalis* leaves may aid in the treatment and prevention of dyslipidemia and perhaps the following atherosclerotic processes because of its strong anti-oxidant activity (Heshmati et al., 2020).

Plants rich in polyphenols are healthy dietary supplements that benefit blood sugar and cholesterol levels in particular (Cicero et al., 2017).

## Significance

Because of its many health benefits and support for a natural, sustainable approach to healthcare, *Melissa officinalis* has enormous medicinal potential. As research progresses, its incorporation into contemporary medicine may broaden, providing safer and easier ways to treat a range of ailments. The plant is a mainstay of herbal therapy with prospective uses in the future of healthcare because of its safety and adaptability.



**Fig. 1. Photo of *Melissa officinalis* (Abdel-Naime et al., 2016)**

## Purpose of Study

The review aims to analyze and assess the present and potential roles of *Melissa officinalis* (MO) in the fields of medicine and clinical sciences. It explores how *M. officinalis* can augment medical practice, research, and patient care. The scope of the review encompasses a broad range of areas, including treatment and therapeutics, and utilization of variety of constituents responsible for numerous pharmacological activities.

# BOTANICAL DESCRIPTION

Common names for the perennial aromatic herb *Melissa officinalis* include lemon balm, honey balm, and bee balm (the Greek word "*Melissa*" means honeybee). Lemon balm grows well in the summer season. White or pinkish-white flowers appear in the summer, while the hairy root structure has numerous lateral roots. The stem of *Melissa officinalis* is quadrilateral or square in shape and can reach a height of 0.5 to 1.5 meters which is a typical characteristic of Lamiacea members. The green, ovate to cordate leaves of MO are arranged in decussate pairs, and they taste and smell like lemons (Fig. 1) (Abdel-Naime et al., 2016).

### Taxonomy of Lemon balm (Weldy et al., 2016):

|  |  |
| --- | --- |
| **Kingdom:** | **Plantae** |
| **Sub kingdom** | Tracheobionta |
| **Super division** | Spermatophyta |
| **Division** | Magnoliophyta |
| **Class** | Magnoliopsida |
| **Sub-class** | Asteridae |
| **Order** | Lamiales |
| **Family** | Lamiaceae |
| **Genus** | *Melissa* L |
| **Species** | *Melissa officinalis*L |

# CHEMICAL CONSTITUENT OF LEMON BALM

The primary components of *M. officinalis*, as determined by chemical investigations, include flavonoids, terpenoids, tannins, essential oils, and phenolic acids (Zarei et al., 2014). Flavonoids (rhamnocitrin, luteolin & quercitin), phenolic compounds (caffeic, protocatechuic, and rosamarinic acid), volatile chemicals (geranial, geraniol, citronellal, and neral) and triterpenes (oleanolic and ursolic acid), are the main active components in *Melissa officinalis* (Shakeri et al., 2016; Miraj et al., 2017). Although

polyphenols are also involved, the essential oil of MO is typically thought for the majority of biological actions as the prime therapeutic agent.

The essential oil of *M. officinalis* smells fresh like lemon and has a pastel yellow tint. It is obtained from the plant's dried or fresh leaves, flowers, and branches using a chemical process or steam distillation (Bağdat & Coşge, 2006).

* 1. **Volatile Components of *Melissa officinalis***

Numerous studies that observed the composition of MO essential oil assert that its main constituents are volatile substances like sesquiterpenes citrals (neral & geranial responsible for strong citrus fragrance) and monoterpenes, citronellal, thymol, geraniol, and β-caryophyllene of different concentrations (Aharizad et al., 2012).

Since *Melissa officinalis* is a member of the family Lamiaceae of plants, produces some amount of volatile oil from its leaves, which is valued for its medicinal qualities.

### Table 1. List of volatile compounds and their percentage composition in the essential oil of *Melissa officinalis* plants (Petrisor et al., 2022)

|  |  |
| --- | --- |
| **Volatile Compounds** | **Amount (%)** |
| **Geranial (CitralA)** | 51.21 |
| **Caryophyllene oxide** | 43.55 |
| **Beta-Caryophyllene** | 29.14 |
| **Neral (CitralB)** | 35.02 |
| **Citronellal** | 20.3 |
| **Geranyl acetate** | 19.3 |
| **Alpha-capaene** | 7.02 |
| **(E)-Caryphyllene** | 6.8 |
| **Alpha-cardinol** | 5.64 |

The method used to produce the essential oil, the conditions required for distillation, the type of plant used, the region's climate, and the MO's level of maturity all affect the existence of different elements and their proportion (Aharizad et al., 2012). However more than 20 different components were found in the two sets of natural oils that were produced through hydraulic distillation from *M. officinalis* cultivated in Iran and Turkey, but the number of major constituents (citral, citronellal, beta-caryophyllenes) was almost similar (Ehsani et al., 2017).

## Triterpenes

There are more than 20,000 different types of triterpenes, they belong to one of the largest

categories of naturally occurring plant compounds and are nonvolatile constituents found in plants (Thimmappa et al., 2014). Ursolic acid (3577 – 11234.97µg/g) and oleanolic acids (915.03-6151.67µg/g) are the primary triterpenoid chemicals identified in *M. officinalis*, although the ethanolic extract of the lemon balm leaves also included one sulfated oleanane, two sulfated ursane type and one oleanane-triterpene (Tantry et al., 2014). Triterpenes connected to the carbohydrate chain and having sulfate chains within their composition are known for stronger biological activity than those attached to an aglycone group (Park et al., 2014).

## Polyphenolic Components

Flavonoids (such as anthocyanins, flavones, isoflavones, rhamnocitrin, luteolin, and quercitrin) and phenolic substances (like protocatechuic, rosamarinic & caffeic acid), a class of secondary metabolites with a variety of biological activities, are included in polyphenolic substances (Barros et al., 2013). Due to the recognized antioxidant activity of these compounds, high concentrations of phenolic content are the main source of lemon balm's medicinal properties. To acquire the proper amount of phenol and, hence, accomplish the phenolic content as well. therapeutic goals, it is imperative to optimize the processing conditions. The origin of the plant affects the phenolic content as well. Rosmarinic, gallic, and chlorogenic acids are more abundant in boiling water extract of *M. officinals* leaves from Bosnia than from Turkey, but cinnamic acid is more abundant in Turkish-origin MO plants (Ibragić et al., 2014).

### Table 2. List of major polyphenolic compounds extracted from *Melissa officinalis* plants (Barros et al., 2013)

composition of the extracts might vary depending on the extraction technique and solvent being used, which has a significant impact on biological activities (Petrisor et al., 2022).

# PHARMACOLOGICAL PROPERTIES

**OF *Melissa officinalis***

## Neuroprotective Effect

The positive impacts of *Melissa officinalis* neurological diseases are believed to be caused by the herb's substantial concentrations of rosmarinic, oleanolic, ursolic, and triterpenoids, which block GABA transport action and elevate levels of this neurotransmitter in the brain(Ibarra et al., 2010).

The potential anti-Alzheimer benefits of MO plants are based on their ability to inhibit the Alzheimer’s disease-related enzymes beta- secretase, casein kinase 1δ, and the enzyme glycogen synthase kinase 3β (Gürbüz et al., 2019). It has also been found that using MO extract reduces muscle tone in individuals with Alzheimer's disease (Pereira et al., 2009).

Byinhibiting HIF-1 alpha & oxidative stress, following apoptosis, *Melissa officinalis* has demonstrated a protective effect against ischemia damage. These findings suggest that *Melissa officinalis* or its components may be used as a possible treatment for conditions affecting the central nervous system as well as a neuroprotective drug to prevent diseases related to oxidative stress (Bayat et al., 2012).

## Anti Inflammatory Effect

As per research, MO essential oil has a strong

 anti-inflammation property, possibly due to

inflammatory disease mediators release inhibition. Prostaglandin and cytokine levels were also decreased by serotonin and histamine (Bounihi et al., 2013).

|  |  |  |
| --- | --- | --- |
|  **Category**  | **Components**  | **Amount(µg/gm)** |
| **Flavonoids** | Rutin | 1462.99 |
|  | Cynaroside | 408.13 |
|  | Isoquercetin | 162.40 |
|  | Quercetin | 153.46 |
|  |  Apigenin  | 84.53  |
| **Phenolic acids** | Rosmarinic acid | 86637.60 |
|  | Caffeic acid | 860.72 |
|  | Caftaric acid | 344.34 |
|  | Chlorogenic acid | 75.529 |
|  |  Gentisic acid  | 60.48  |

Although *Melissa officinalis* is a plant with a high concentration of polyphenolic chemicals, the

According to published studies, the anti- nociceptive & anti inflammatory action of *Melissa officinalis* extract is attributed to flavonoids and terpenoids, specifically rosmarinic acid (RA). *Melissa officinalis* (MO) compounds inhibit the cyclooxygenase enzyme, which decreases the production of prostaglandins and inflammatory cytokines in response to inflammatory stimuli, as well as the monoamine oxidase enzyme, which prevents catecholamine degradation (Zarei et al., 2015). The flavonoids quercetin, luteolin, and

apigenin, phenolic components of MO with immune-modulating activities can decrease inflammation and may prevent cardiac tissue remodeling in animal models of myocarditis (Milenković et al., 2010; Wu et al., 2020). By reducing the synthesis of inflammatory cytokines in CVB3-infected cells, luteolin was found to be useful in treating myocarditis caused by the coxsackievirus B3 (Wu et al., 2020).

## Cardioprotective Effect

Joukar and Asadipour (2015) examined the pharmacological impact of MO on ventricular arrhythmias in rats. Findings from the research exhibited aqueous MO extract works through a variety of mechanisms and have a milder antiarrhythmic impact than the common antiarrhythmic drug Amiodarone (Joukar & Asadipour, 2015).

Ethanolic extract of MO was shown to exhibit cardioprotective action against myocardial infarction and coronary heart damage after 5 days of reperfusion in an *invivo* rat model of localized coronary heart ischemia. Due to its antioxidant characteristics, which may result from the scavenging of free radicals, cinnamic acid is thought to be responsible for cardioprotective and antiarrhythmic effects in *M. officinalis* extract (Sedighi et al., 2019).

Antiarrhythmic effects of ethanolic MO extract have also been investigated in the CaCl2 induced rat model by Akhondali *et al.* (2015). The study showed a decreased prevalence of ventricular arrhythmias at a dose of 200mg/kg of MO extract (Akhondali et al., 2015). Ameliorating effects of MO have been seen against (Doxorubicin) DOX-induced cardiovascular damage in rats that occurs due to a decrease in oxidative stress, inflammatory process, and apoptosis in rat hearts. The positive effects of the MO extract could be due to the synergistic associations between phenolic chemicals and other triterpene groups in MO (Hamza et al., 2016).

## Hypolipidemic Effects

In the rat model of hyperlipidemia caused by a high-sugar, high-fat diet, MO extract considerably decreases plasma levels of total lipids and cholesterol. The hypolipidemic effects of *M. officinalis* extract may be attributed to the synergistic impact of the substances in MO, such as rosmarinic, ursolic, and oleanolic acids on

blood lipid levels (Yuliang et al., 2015; Guo et al., 2020).

Hypolipidemic effects of *Melissa officinalis* extract were observed when administered 1000 mg, a recommended dose (TID) for 2 months in patients with hyperlipidemia (Jun et al., 2012). In individuals with type 2 diabetes, *Mellissa officinalis* (MO) safely and effectively lowers lipoprotein levels, Apo B/Apo A-I &Apo A-I, which are important indicators of risk for CVD (cardiovascular disease) (Asadi et al., 2018).

Evaluation of medicinal lemon balm for use in angina pectoris showed a greater percentage of cardiac ejection, reduced plasma lactate- dehydrogenase levels, increased NO (nitric oxide) levels, & lower diastolic as well as systolic blood pressure compared to the control group, also preventing the deposition of fats resulting in arteriolar dilatation (Javid et al., 2018).

## Vasorelaxant Effect

According to the research, the study showed that the nitric oxide pathway potentially with the prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) pathways is the physiological process by which the aqueous extract of MO dilates blood arteries (Yui et al., 2017).

## Anti-depressant Effect

Different dosages of 300,100 & 30mg/kg ethanolic MO extract were given orally to Wistar rats over the course of ten days to evaluate the animals' behavior in elevated plus-maze, open field tests, and forced swimming. Antidepressant effect of MO ethanolic extract was quite pronounced in rats rather than in those treated with diazepam (Mirabi et al., 2017). Additionally, it was reported that the ant-depressive actions of lemon balm can be carried out by modulating the 5-HT cycle in the regions of the brain involving serotonin in the transmission of nerve impulses (Lin et al., 2015).

## Anxiolytic Effect

Literature review showed an anti-anxiety effect of MO depends on the administered dose, and the bioactive compounds involved pentacyclic triterpenes, oleanolic, ursolic, & rosmarinic acid (Dastmalchi et al., 2008). The primary constituent of the *Melissa officinalis* plant, Rosmarinic acid has been associated with many Gama

Aminobutyric Acid Transaminase (GABAT) inhibitory therapeutic activities. *M. officinalis and*

*P. caerulea*were administered in vivo, and it was shown that the synergistic interaction had anxiolytic effects by lowering corticosterone levels (a physiological stress mediator) (Shakeri et al., 2016; Moacă et al., 2018).

## Hypnotic Effect

In a previous study, a combination of *Melissa officinalis* and *Valeriana officinalis has* shown a positive effect on sleep disturbances among women going through menopause (Taavoni & Haghani, 2013).

MO extract (400, 800 mg/kg) is found to be beneficial while considerably decreasing the time needed to fall asleep and increasing the amount of time spent sleeping in a mouse-based investigation. Additionally, was demonstrated the combination of lavender extract (*Lavandula angustifolia*) and *M. officinalis* extract had a synergistic impact on the duration required to fall asleep and stay asleep which could be important in treating insomnia (Hajhashemi & Safaei, 2015).

## Antispasmodic Effect

Rosmarinic acid, an active constituent of *Melissa officinalis* appears to have anti-nociceptive ability. The effectiveness of *Melissa officinalis* in treating infantile colic has been evaluated and found to have positive effects(Wölbling & Leonhardt, 1994).

Research suggests that in rats with irritable bowel syndrome, hydro-alcoholic lemon balm extract may be able to lessen visceral hypersensitivity (Dolatabadi et al., 2018). In addition, a single dosage of 150, 300, and 450 mg/kg of methanolic MO leaf extract helps treat rat stomach ulcers. The suggested strategy was to decrease the production of malondialdehyde, minimize lipid peroxidation in cell membranes, and increase the functions of superoxide dismutase and glutathione peroxidase (Saberi et al., 2016).

## Anti-tumor Effect

Magalhes *et al*. (2018) investigated the antitumor properties of this natural herb on lung cancer stem cells using a comparative investigation of five distinct *M. officinalis* extracts (Magalhães et al., 2018). Rosmaricinic acid, which has great

penetration ability, is found in the MO ethanolic extract, which shows a suppressive effect on the proliferation of malignant cells. These primary results of the study further validate lemon balm as a reservoir of potentially anticancer bioactive compounds.

In human colon carcinoma cells, the ethanolic leaf extract of *Melissa officinalis* was tested for its anti-proliferative and pro-apoptotic properties. It has been found that *Melissa officinalis* extract prevents cells of colon cancer from proliferating and triggers apoptosis through ROS (reactive oxygen species) production (Weidner et al., 2015).

## Antimicrobial Effect

*In vitro* testing showed that Gram-negative& Gram-positive bacteria, fungi, and yeasts were all inhibited in growth by an essential oil isolated from leaves of *Melissa officinalis* (Ghiulai et al., 2020).

## Anti-fungal Effect

Good to moderate anti-fungal MO extract activity and other species of the Lamiaceae family have been reported (Araújo et al., 2019).

Essential oil from lemon balm is the potential anti-fungal agent against *Bcinera, Pexpansum*, and *Rstolonifer* species as this kind of essential oil is biodegradable and has no lasting effects on the environment (El Ouadi et al., 2017).

## Anti-viral Effect

*In vitro*, testing conducted by Astani *et al.* (2018) demonstrated the antiviral properties of rosamarinic acid and aqueous extract of lemon balm leaves by inhibiting the attachment of herpes simplex virus-type 1 (HSV-1) in the host and the entry of cells as well (Astani et al., 2014). In addition, it has been observed that concentrated methanolic lemon balm leaf extract has an inhibitory impact on enterovirus 71 (EV71) (Chen et al., 2017).

## Anti-thyroid Effect

Aqueous extracts of *M. officinalis* leaves have an antithyroid action, according to in vitro studies. Iodothyronine deiodinase from rat’s liver microsome was used to observe the conversion of T4 to T3, depending on the dosage. Caffeic, rosmarinic, and chlorogenic acids present in MO

extract are responsible for the effects (Kaplan & Dosiou, 2021).

## Analgesic Effect

The study has shown that giving hydroalcoholic extract of *Melissa officinalis* intrathecally might substantially reduce the discomfort that male Wister rats experienced after being exposed to hot water and formalin (Rastegarian et al., 2020).

# CONCLUSION

This review has enlightened the beneficial effects of *Melissa officinalis* in treating a variety of abnormal conditions thus providing possible evidence that *Melissa officinalis* could be used as an alternate treatment option for combating numerous disorders due to the presence of vast amount of phytochemical constituents contributing to its various therapeutic potential.

# FUTURE PROSPECTS

Further experimental and clinical studies could be designed in the future to explore other potential molecular pathways involved in disease pathogenesis that could be the future therapeutic approach in the treatment and prevention of cardiometabolic diseases.

It is also recommended that the toxicity profile of *Melissa officinalis* be investigated at various doses before moving on to clinical testing.

# CONSENT AND ETHICAL APPROVAL

It is not applicable.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

1. Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text- to-image generators have been used during writing or editing of this manuscript.

# COMPETING INTERESTS

Authors have declared that no competing interests exist.

# REFERENCES

Abdel-Naime, W. A., Fahim, J. R., Fouad, M. A., & Kamel, M. S. (2016). Botanical studies of the leaf of *Melissa officinalis* L., Family: Labiatae, cultivated in Egypt. *Journal of*

*Pharmacognosy and Phytochemistry, 5*(6), 98.

Abdel-Naime, W. A., Fahim, J. R., Fouad, M. A., & Kamel, M. S. (2016). Botanical studies of the leaf of *Melissa officinalis* L., Family: Labiatae, cultivated in Egypt. *Journal of Pharmacognosy and Phytochemistry, 5*(6), 98.

Aharizad, S., Rahimi, M. H., Moghadam, M., & Mohebalipour, N. (2012). Study of genetic diversity in lemon balm (*Melissa officinalis* L.) populations based on morphological traits and essential oils content. *Annals of Biological Research, 3*(12), 5748-5753. https://scholarsresearchlibrary.com

Akhondali, Z., Dianat, M., & Radan, M. (2015). Negative chronotropic and antidysrhythmic effects of hydroalcoholic extract of lemon balm (*Melissa officinalis* L.) on CaCl2- induced arrhythmias in rats. *Electronic Physician*, 7(1), 971-976.

https://doi.org/10.14661/2015.971-976 Araújo, S. G., Lima, W. G., Pinto, M. E., Morais,

M. Í., de Sá, N. P., Johann, S., Rosa, C. A., & dos Santos Lima, L. A. (2019). Pharmacological prospection in-vitro of Lamiaceae species against human pathogenic fungi associated with invasive infections. *Biocatalysis and Agricultural Biotechnology*, 21, 101345.

https://doi.org/10.1016/j.bcab.2019.101345 Asadi, A., Safari, M., Malek, M., Hosseini, A. F., Rezazadeh, S., Rajab, A., Shidfar, S., & Hosseini, S. (2018). Safety and efficacy of *Melissa officinalis* (lemon balm) on ApoA-I,

Apo B, lipid ratio and ICAM-1 in type 2 diabetes patients: A randomized, double- blinded clinical trial. *Complementary Therapies in Medicine*, 40, 83-88.

https://doi.org/10.1016/j.ctim.2018.07.015 Astani, A., Heidary Navid, M., & Schnitzler, P.

(2014). Attachment and penetration of acyclovir‐resistant herpes simplex virus are inhibited by *Melissa officinalis* extract. *Phytotherapy Research*, 28(10), 1547-

1552. https://doi.org/10.1002/ptr.5166 Bağdat, R. B., & Coşge, B. (2006). The essential

oil of lemon balm (*Melissa officinalis* L.), its components and using fields. *Anadolu Tarım Bilimleri Dergisi, 21*(1), 116-121.

https://doi.org/10.7161/anajas.2006.21.1.1 16-121

Barros, L., Dueñas, M., Dias, M. I., Sousa, M. J., Santos-Buelga, C., & Ferreira, I. C. (2013). Phenolic profiles of cultivated, in vitro cultured and commercial samples of *Melissa officinalis* L. infusions. *Food*

*Chemistry, 136*(1), 1-8.

https://doi.org/10.1016/j.foodchem.2012.07

.107

Barros, L., Dueñas, M., Dias, M. I., Sousa, M. J., Santos-Buelga, C., & Ferreira, I. C. (2013). Phenolic profiles of cultivated, in vitro cultured and commercial samples of *Melissa officinalis* L. infusions. *Food Chemistry, 136*(1), 1-8.

https://doi.org/10.1016/j.foodchem.2012.07

.107

Bayat, M., Azami Tameh, A., Hossein Ghahremani, M., Akbari, M., Mehr, S. E., Khanavi, M., & Hassanzadeh, G. (2012). Neuroprotective properties of *Melissa officinalis* after hypoxic-ischemic injury both in vitro and in vivo. *DARU Journal of Pharmaceutical Sciences, 20*, 1-0.

Bounihi, A., Hajjaj, G., Alnamer, R., Cherrah, Y., & Zellou, A. (2013). In vivo potential anti- inflammatory activity of *Melissa officinalis*

L. essential oil. *Advances in Pharmacological Sciences.*

Chen, S. G., Leu, Y. L., Cheng, M. L., Ting, S.

C., Liu, C. C., Wang, S. D., Yang, C. H.,

Hung, C. Y., Sakurai, H., Chen, K. H., & Ho, H. Y. (2017). Anti-enterovirus 71

activities of *Melissa officinalis* extract and its biologically active constituent rosmarinic acid. *Scientific Reports*, 7(1), 12264.

Cicero, A. F., Fogacci, F., & Colletti, A. (2017). Food and plant bioactives for reducing cardiometabolic disease risk: An evidence- based approach. *Food & Function, 8*(6), 2076-2088.

https://doi.org/10.1039/c7fo00178a Dastmalchi, K., Dorman, H. D., Oinonen, P. P.,

Darwis, Y., Laakso, I., & Hiltunen, R. (2008). Chemical composition and in vitro antioxidative activity of a lemon balm (*Melissa officinalis* L.) extract. *LWT - Food Science and Technology*, 41(3), 391-400. https://doi.org/10.1016/j.lwt.2007.03.007

Dolatabadi, F., Abdolghaffari, A. H., Farzaei, M. H., Baeeri, M., Ziarani, F. S., Eslami, M., Abdollahi, M., & Rahimi, R. (2018). The protective effect of *Melissa officinalis* L. in visceral hypersensitivity in rats using 2

models of acid-induced colitis and stress- induced irritable bowel syndrome: a possible role of nitric oxide pathway. *Journal of Neurogastroenterology and Motility*, 24(3), 490.

https://doi.org/10.5056/jnm17035

Dragičić, N., Jakovljević, V., Andjić, M., Jeremić, J., Srejović, I., Ranković, M., Tomović, M., Nikolić-Turnić, T., Svistunov, A., Bolevich,

S., & Milosavljević, I. (2021). *Melissa officinalis* L. as a nutritional strategy for cardioprotection. *Frontiers in Physiology, 12*, 661778.

https://doi.org/10.3389/fphys.2021.661778 Ehsani, A., Alizadeh, O., Hashemi, M., Afshari,

A., & Aminzare, M. (2017). Phytochemical, antioxidant and antibacterial properties of *Melissa officinalis* and *Dracocephalum moldavica* essential oils. *Veterinary Research Forum, 8*, 223–229.

El Ouadi, Y., Manssouri, M., Bouyanzer, A., Majidi, L., Bendaif, H., Elmsellem, H., Shariati, M. A., Melhaoui, A., & Hammouti,

B. (2017). Essential oil composition and antifungal activity of *Melissa officinalis* originating from north-east Morocco, against postharvest phytopathogenic fungi in apples. *Microbial Pathogenesis*, 107, 321-326.

https://doi.org/10.1016/j.micpath.2017.04.0 04

Emamghoreishi, M., & Talebianpour, M. S. (2015). Antidepressant effect of *Melissa officinalis* in the forced swimming test. *DARU Journal of Pharmaceutical Sciences, 17*(1), 42-47.

https://sid.ir/paper/275489/en

Ghiulai, R., Avram, S., Stoian, D., Pavel, I. Z., Coricovac, D., Oprean, C., Vlase, L., Farcas, C., Mioc, M., Minda, D., Motoc, A. (2020). Lemon balm extracts prevent breast cancer progression in vitro and in ovo on chorioallantoic membrane assay. *Evidence-Based Complementary and Alternative Medicine*, 2020.

https://doi.org/10.1155/2020/6489159

Guo, C., Shangguan, Y., Zhang, M., Ruan, Y.,

Xue, G., Ma, J., Yang, J., & Qiu, L. (2020).

Rosmarinic acid alleviates ethanol-induced lipid accumulation by repressing fatty acid biosynthesis. *Food & Function*, 11(3), 2094-2106.

https://doi.org/10.1039/C9FO02357G Gürbüz, P., Martinez, A., Pérez, C., Martínez-

González, L., Göger, F., & Ayran, İ. (2019). Potential anti-Alzheimer effects of selected Lamiaceae plants through polypharmacology on glycogen synthase kinase-3β, β-secretase, and casein kinase 1δ. *Industrial Crops and Products, 138*, 111431.

https://doi.org/10.1016/j.indcrop.2019.05.0 80

Hajhashemi, V., & Safaei, A. (2015). Hypnotic effect of *Coriandrum sativum*, *Ziziphus jujuba*, *Lavandula angustifolia*, and *Melissa*

*officinalis* extracts in mice. *Research in Pharmaceutical Sciences*, 10(6), 477.

Hamza, A. A., Ahmed, M. M., Elwey, H. M., & Amin, A. (2016). *Melissa officinalis* protects against doxorubicin-induced cardiotoxicity in rats and potentiates its anticancer activity on MCF-7 cells. *PLOS ONE*, 11(11), e0167049.

https://doi.org/10.1371/journal.pone.01670 49

Heshmati, J., Morvaridzadeh, M., Sepidarkish, M., Fazelian, S., Rahimlou, M., Omidi, A., Palmowski, A., Asadi, A., & Shidfar, F. (2020). Effects of *Melissa officinalis* (Lemon balm) on cardio-metabolic outcomes: A systematic review and meta- analysis. *Phytotherapy Research, 34*(12), 3113–3123.

https://doi.org/10.1002/ptr.6744

Ibarra, A., Feuillere, N., Roller, M., Lesburgere, E., & Beracochea, D. (2010). Effects of chronic administration of *Melissa officinalis*

L. extract on anxiety-like reactivity and on circadian and exploratory activities in mice. *Phytomedicine, 17*(6), 397-403.

https://doi.org/10.1016/j.phymed.2010.01.0 12

Ibragić, S., Salihović, M., Tahirović, I., & Toromanović, J. (2014). Quantification of some phenolic acids in the leaves of *Melissa officinalis* L. from Turkey and Bosnia. *Bulletin of Chemical Technology, Bosnia & Herzegovina, 42*, 47-50.

Javid, A. Z., Haybar, H., Dehghan, P., Haghighizadeh, M. H., Mohaghegh, S. M., Ravanbakhsh, M., Mohammadzadeh, A. (2018). The effects of *Melissa officinalis* (lemon balm) in chronic stable angina on serum biomarkers of oxidative stress, inflammation and lipid profile. *Asia Pacific Journal of Clinical Nutrition*, 27(4), 785-

791.

Joukar, S., & Asadipour, H. (2015). Evaluation of *Melissa officinalis* (Lemon Balm) effects on heart electrical system. *Research in Cardiovascular Medicine*, 4(2), e27013. https://doi.org/10.5812/cardiovascmed.4(2) 2015.27013

Jun, H. J., Lee, J. H., Jia, Y., Hoang, M. H.,

Byun, H., Kim, K. H., Lee, S. J. (2012).

*Melissa officinalis* essential oil reduces plasma triglycerides in human apolipoprotein E2 transgenic mice by inhibiting sterol regulatory element-binding protein-1c–dependent fatty acid synthesis. *The Journal of Nutrition*, 142(3), 432-440. https://doi.org/10.3945/jn.111.152538

Kaplan, D., & Dosiou, C. (2021). Two cases of Graves’ hyperthyroidism treated with homeopathic remedies containing herbal extracts from *Lycopus* spp. and *Melissa officinalis*. *Journal of the Endocrine Society*, 5(Supplement\_1), A971. https://doi.org/10.1210/jendso/bvab048.19 85

Lin, S. H., Chou, M. L., Chen, W. C., Lai, Y. S., Lu, K. H., Hao, C. W., & Sheen, L. Y.

(2015). A medicinal herb, *Melissa officinalis* L. ameliorates depressive-like behavior of rats in the forced swimming test via regulating the serotonergic neurotransmitter. *Journal of Ethnopharmacology*, 175, 266-272.

https://doi.org/10.1016/j.jep.2015.09.018 Magalhães, D. B., Castro, I., Lopes-Rodrigues,

V., Pereira, J. M., Barros, L., Ferreira, I. C., Xavier, C. P., & Vasconcelos, M. H. (2018). *Melissa officinalis* L. ethanolic extract inhibits the growth of a lung cancer cell line by interfering with the cell cycle and inducing apoptosis. *Food & Function*, 9(6), 3134-3142.

https://doi.org/10.1039/C8FO00446C Milenković, M., Arsenović-Ranin, N., Stojić-

Vukanić, Z., Bufan, B., Vučićević, D., & Jančić, I. (2010). Quercetin ameliorates experimental autoimmune myocarditis in rats. *Journal of Pharmacy and Pharmaceutical Sciences, 13*(3), 311-319. https://doi.org/10.18433/J3VS3S

Mirabi, P., Namdari, M., Alamolhoda, S., & Mojab, F. (2017). The effect of *Melissa officinalis* extract on the severity of primary dysmenorrhea. *Iranian Journal of Pharmaceutical Research: IJPR*, 16(Suppl), 171.

Miraj, S., Rafieian-Kopaei, M., & Kiani, S. (2017). *Melissa officinalis* L: A review study with an antioxidant prospective. *Journal of Evidence-Based Complementary & Alternative Medicine, 22*(3), 385-394.

https://doi.org/10.1177/2156587216663433 Miraj, S., Rafieian-Kopaei, M., & Kiani, S. (2017). *Melissa officinalis* L: A review study with an antioxidant prospective. *Journal of Evidence-Based Complementary & Alternative Medicine, 22*(3), 385-394.

https://doi.org/10.1177/2156587216663433 Moacă, E. A., Farcaş, C., Ghiţu, A., Coricovac, D., Popovici, R., Cărăba-Meiţă, N. L., Ardelean, F., Antal, D. S., Dehelean, C., & Avram, Ş. (2018). A comparative study of *Melissa officinalis* leaves and stems ethanolic extracts in terms of antioxidant,

cytotoxic, and antiproliferative potential. *Evidence-Based Complementary and Alternative Medicine*, 2018.

https://doi.org/10.1155/2018/7860456 Moradkhani, H., Sargsyan, E., Bibak, H., Naseri,

B., Sadat-Hosseini, M., Fayazi-Barjin, A., & Meftahizade, H. (2010). *Melissa officinalis* L., a valuable medicinal plant. *Journal of Medicinal Plants Research, 4*, 2753-2759. https://academicjournals.org/JMPR

Park, J. I., Bae, H. R., Kim, C. G., Stonik, V. A., & Kwak, J. Y. (2014). Relationships between chemical structures and functions of triterpene glycosides isolated from sea cucumbers. *Frontiers in Chemistry, 2*, 77. https://doi.org/10.3389/fchem.2014.00077

Pereira, R. P., Fachinetto, R., de Souza Prestes, A., Puntel, R. L., Santos da Silva, G. N., Heinzmann, B. M., Boschetti, T. K., Athayde, M. L., Bürger, M. E., Morel, A. F., & Morsch, V. M. (2009). Antioxidant effects of different extracts from *Melissa officinalis*, *Matricaria recutita*, and *Cymbopogon citratus*. *Neurochemical Research, 34*, 973-983.

Petrisor, G., Motelica, L., Crăciun, L. N., Oprea,

O. C., Ficai, D., & Ficai, A. (2022). *Melissa officinalis*: Composition, pharmacological effects and derived release systems—A review. *International Journal of Molecular Sciences, 23*(7), 3591.

https://doi.org/10.3390/ijms23073591 Rasmussen, P. (2011). Lemon balm–*Melissa*

*officinalis*; also known as lemon balm, bee balm, garden balm, *Melissa*, melissengeist. *Journal of Primary Health Care, 3*(2), 165-

166. https://doi.org/10.1071/hc11165 Rastegarian, A., Abedi, H., Jahromi, H. K., Zarei,

S., Nematollahi, A., Mansouri, E., &Sameni, H. (2020). Analgesic effect of intrathecal *Melissa officinalis* in the rat model of hot-water and formalin-induced pain. *Journal of Acupuncture and Meridian Studies*, 13(1), 19-24.

https://doi.org/10.1016/j.jams.2019.11.001 Saberi, A., Abbasloo, E., Sepehri, G.,

Yazdanpanah, M., Mirkamandari, E., Sheibani, V., Safi, Z. (2016). The effects of methanolic extract of *Melissa officinalis* on experimental gastric ulcers in rats. *Iranian Red Crescent Medical Journal*, 18(7). https://doi.org/10.5812/ircmj.24271

Sedighi, M., Faghihi, M., Rafieian-Kopaei, M., Rasoulian, B., & Nazari, A. (2019). Cardioprotective effect of ethanolic leaf extract of *Melissa officinalis* L against regional ischemia-induced arrhythmia and

heart injury after five days of reperfusion in rats. *Iranian Journal of Pharmaceutical Research: IJPR*, 18(3), 1530.

https://doi.org/10.22037/ijpr.2019.1100761 Shakeri, A., Sahebkar, A., & Javadi, B. (2016).

*Melissa officinalis* L.–A review of its traditional uses, phytochemistry and pharmacology. *Journal of Ethnopharmacology, 188*, 204-228.

https://doi.org/10.1016/j.jep.2016.05.010 Shakeri, A., Sahebkar, A., & Javadi, B. (2016).

*Melissa officinalis* L. – A review of its traditional uses, phytochemistry, and pharmacology. *Journal of Ethnopharmacology*, 188, 204-228.

https://doi.org/10.1016/j.jep.2016.05.010 Taavoni, S., & Haghani, H. (2013).

Valerian/lemon balm use for sleep disorders during menopause. *Complementary Therapies in Clinical Practice*, 19(4), 193-196.

https://doi.org/10.1016/j.ctcp.2013.07.002 Tantry, M. A., Bhat, G. A., Idris, A., Dar, J. A.,

Yousef Al Omar, S., Masoodi, K. Z., Ganai,

B. A., Kamili, A. N., Shawl, A. S. (2014).

Sulfated triterpenes from lemon balm.

*Helvetica Chimica Acta, 97*(11), 1497- 1506.

https://doi.org/10.1002/hlca.201400001 Thimmappa, R., Geisler, K., Louveau, T.,

O'Maille, P., & Osbourn, A. (2014). Triterpene biosynthesis in plants. *Annual Review of Plant Biology, 65*, 225-257.

https://doi.org/10.1146/annurev-arplant- 050312-120229

Weidner, C., Rousseau, M., Plauth, A., Wowro,

S. J., Fischer, C., Abdel-Aziz, H., Sauer, S. (2015). *Melissa officinalis* extract induces apoptosis and inhibits proliferation in colon cancer cells through formation of reactive oxygen species. *Phytomedicine*, 22(2), 262-270.

https://doi.org/10.1016/j.phymed.2014.12.0 08

Weldy, T., Werier, D., & Nelson, A. (2016). *New York Flora Atlas*. [SM Landry and KN Campbell (original application development), USF Water Institute]. New York Flora Association.

Wölbling, R. H., & Leonhardt, K. (1994). Local therapy of herpes simplex with dried extract from *Melissa officinalis*. *Phytomedicine*, 1(1), 25-31.

https://doi.org/10.1016/S0944- 7113(11)80019-X

Wu, S., Wang, H. Q., Guo, T. T., & Li, Y. H.

(2020). Luteolin inhibits CVB3 replication

through inhibiting inflammation. *Journal of Asian Natural Products Research*, 22(8), 762-773.

https://doi.org/10.1080/10286020.2019.164 2329

Yui, S., Fujiwara, S., Harada, K., Motoike- Hamura, M., Sakai, M., Matsubara, S., &Miyazaki, K. (2017). Beneficial effects of lemon balm leaf extract on in vitro glycation of proteins, arterial stiffness, and skin elasticity in healthy adults. *Journal of Nutritional Science and Vitaminology*, 63(1), 59-68.

https://doi.org/10.3177/jnsv.63.59

Yuliang, W., Zejian, W., Hanlin, S., Ming, Y., & Kexuan, T. (2015). The hypolipidemic

effect of artesunate and ursolic acid in rats. *Pakistan Journal of Pharmaceutical Sciences*, 28(3).

Zarei, A., Ashtiyani, S. C., Taheri, S., & Rasekh,

F. (2014). Comparison between effects of different doses of *Melissa officinalis* and atorvastatin on the activity of liver enzymes in hypercholesterolemia rats. *Avicenna Journal of Phytomedicine, 4*, 15-23.

Zarei, A., Changizi-Ashtiyani, S., Taheri, S., & Hosseini, N. (2015). A brief overview of the effects of *Melissa officinalis* L. extract on the function of various body organs. *Zahedan Journal of Research in Medical Sciences, 17*(7).

https://doi.org/10.17795/zjrms1007