

Correction

Correction: Wissam Zam *et al.* An Updated Review on The Properties of *Melissa officinalis* L.: Not Exclusively Anti-anxiety. Frontiers in Bioscience-Scholar. 2022; 14: 16

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Academic Editor: Gustavo Caetano-Anollés

Submitted: 4 August 2022 Accepted: 24 November 2022 Published: 7 December 2022

The authors would like to make a correction to the article [1]. The authors clarify that the reference [2] in the Fig. 5 caption is not cited in this review article in error. We apologise to readers for any inconvenience caused and state that the scientific conclusions are unaffected. This correction was approved by the Academic Editor. The references in the article have also been updated.

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- [1] Zam W, Quispe C, Sharifi-Rad J, López MD, Schoebitz M, Martorell M, *et al.* An Updated Review on the Properties of *Melissa officinalis* L.: Not Exclusively Anti-anxiety. Frontiers in Bioscience-Scholar. 2022; 14: 16.
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Review

An Updated Review on The Properties of *Melissa officinalis* L.: Not Exclusively Anti-anxiety

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Academic Editor: Gustavo Caetano-Anollés

Submitted: 2 February 2022 Revised: 30 March 2022 Accepted: 11 April 2022 Published: 7 June 2022

Abstract

Melissa officinalis L. is a plant of the Lamiaceae family known in numerous countries for its medicinal activities. This plant has been used since ancient times to treat different disorders, including gastrointestinal, cardiovascular, neurological, psychological conditions. *M. officinalis* contains several phytochemicals such as phenolic acids, flavonoids, terpenoids, and many others at the basis of its pharmacological activities. Indeed, the plant can have antioxidant, anti-inflammatory, antispasmodic, antimicrobial, neuroprotective, nephroprotective, antinociceptive effects. Given its consolidated use, *M. officinalis* has also been experimented with clinical settings, demonstrating interesting properties against different human diseases, such as anxiety, sleeping difficulties, palpitation, hypertension, depression, dementia, infantile colic, bruxism, metabolic problems, Alzheimer’s disease, and sexual disorders. As for any natural compound, drug, or plant extract, also *M. officinalis* can have adverse effects, even though the reported events are very rare and the plant can be considered substantially safe. This review has been prepared with a specific research strategy, interrogating different databases with the keyword *M. officinalis*. Moreover, this work analyzes the properties of this plant updating currently available literature, with a special emphasis on human studies.

Keywords: *Melissa officinalis* L.; lemon balm; phytotherapy; phytochemicals; health properties; clinical trials

1. Introduction

In today’s world, the prevalence of anxiety disorders has skyrocketed. Anxiolytics can be used to treat these illnesses, although they can have some negative side effects despite their effectiveness. Because of the lack of understanding about drug interactions and possible harmful effects, traditional medicine poses a serious risk to public health. Plants’ clinical efficacy must be evaluated in research investigations. *Melissa officinalis* L., popularly known as lemon balm, is utilized in traditional medicine

for its effects on CNS processes such as sedation and memory improvement and additionally possess various health benefits if consumed in optimum concentration but unfortunately, no comprehensive compilation has been done so far [1]. The majority of beneficial effects of the Therefore, it is important to present complete information of *Melissa officinalis* L. are due to volatile oils, triterpenes, and phenolic compounds.

An increasing body of evidence suggests that this plant may have therapeutic potential in the management of dis-



orders such as diabetes and Alzheimer's disease. It also contains antioxidant, antibacterial, and anti-inflammatory properties [2,3]. The low toxicity and lack of side effects of this plant have been proven in several investigations utilizing different experimental models [4]. But if the plant extracts are not used optimally, they may exert toxicity both in cell and animal models. In the clinical trials, the effect of *M. officinalis* extracts has been proved evaluated on a variety of diseases, mainly related to neurological disorders, i.e., anxiety and sleeping difficulties, but also metabolic problems and infantile colic and shown to have positive effects. The present review was aimed to compile information on botany and phytochemistry, traditional medicinal, and ethnopharmacological uses of *M. officinalis*, and also various clinical aspects and biomedical properties of this well-known plant are discussed.

This review has been prepared through an interrogation of different databases, such as Chrocan library, Embase-Elsevier, Google Scholar, Ovid, PubMed, Science Direct, SciFinder, Scopus, Web of Science. Both articles, papers, and books have been considered, while the search strategy was based on the keyword *Melissa officinalis*, in addition to its English translation or common names as "common balm", "honey balm", "lemon balm", "melissa balm", "sweet balm".

2. Botany of *Melissa officinalis*

Melissa officinalis can be taxonomically classified as follows: Kingdom: *Plantae*; Division: *Tracheophyta*; Sub-division: *Spermatophyta*; Class: *Magnoliopsida*; Super-order: *Asteranae*; Order: *Lamiales*; Family: *Lamiaceae*; Genus: *Melissa*; Species: *Melissa officinalis* L. [5].

From a botanical point of view, *Melissa officinalis* L. (Greek word "*Melissa*"—honeybee) is the only acceptable name for the plant and possesses different accepted varieties, i.e., *M. officinalis* var. *altissima* (Sm.) K.Koch, *M. officinalis* var. *cordifolia* (Pers.) K.Koch, *M. officinalis* var. *foliosa* Briq., *M. officinalis* var. *graveolens* (Host) Nyman, *M. officinalis* var. *hirsuta* K. Koch, *M. officinalis* var. *romana* (Mill.) Woodv. and *M. officinalis* var. *villosa* Benth [6,7]. *M. officinalis* L. is also known as lemon balm, bee balm, sweet balm, common balm, honey balm [5,6].

There is also an infraspecific taxon of the species *M. officinalis* which are naturally expended in our wild flora: *M. officinalis* ssp. *altissima* (Sm.) Arcang., *M. officinalis* ssp. *officinalis*, *M. officinalis* subsp. *inodora* Bornm [8,9]. *M. officinalis* shows economic significance because there is an increase in growth terrain and novel varieties exploration [9].

A haploid base number of *M. officinalis* of $x = 16$ chromosomes is likely, diploid genotypes with $2n = 2 \times = 32$ chromosomes; tetraploid $2n = 4 \times = 64$ chromosomes, and triploid $2n = 3 \times = 48$ chromosomes [9,10]. *M. officinalis* is a perennial shrubby plant, with a height of 30–150 cm with fluffy hairs surrounding all parts [8,11]. The stem is

erect, branched, usually glabrous, and quadrangular. The leaves are in decussate pairs, petiolate, soft, ovate, 2–8 cm long, 3 cm broad, the upper cuneate, the lower cordate at base, crenate-toothed, subglabrous, sometimes with glandular hairs or punctuate glands beneath. The leaf surface is gross and deeply streaked, and the leaf edge is scalloped or toothed [6,8]. Flowers are commonly white or pale pink with small clusters of 4 to 12 blossoms in the summer. They have a peculiar lemon-like flavor and fragrance [6,8]. The subspecies of *M. officinalis* can be differentiated through the shape of calyx and the density of different types of hairs. The middle tooth of the three upper lip teeth of the fruiting calyx is approximately three-sided for ssp. *officinalis* while it is decent, shorten, or emarginated for ssp. *altissima* [9].

M. officinalis is a cross-pollinating species and has complete flowers with petals. Two stamens and four-lobed ovaries can give rise to 1–4 nutlets. The seeds are very small about 1–1.5 mm long, with ovate dark brown or black color. The weight of seeds is 0.5 to 0.7 g and they can be considered fragile as a long storage period (5 years) can induce a decrease in germination vigor [6,8]. The plant possesses a highly branched root system, which guarantees the plant excellent adaptive capabilities; the upper parts of the plant perish at the beginning of the winter, while in spring new saplings re-emerge from the roots [7]. *M. officinalis* is cultivated all over the world, with the Mediterranean basin or Western Asia are considered as the area of origin [9]. There is a different opinion that suggests this plant is originated from a more wide area comprising South and Central Europe, Northern Africa, the Caucasus, and Northern Iran [11,12]. *M. officinalis* occurs naturally in sandy and loamy fertile soils but sometimes can grow on moist wasteland from sea level to the mountains [5,8,12]. The plant prefers well-drained soils with a pH range from 5 to 7, it can grow in full sun, but also partial shade. When the plant grows in semi-shade, it produces bigger leaves compared to the sunny situation. This means that *M. officinalis* can promptly develop in a temperate environment (15 to 35 °C) necessitating at least 500 to 600 mm precipitation during all growing seasons. It suffers from drought, particularly in the establishment year, however after the root system is developed, requires a reduced amount of water [8]. The plant can be considered for easy cultivation and this reason can be suggested for beginners. In addition, given its adaptive capacities and strength, some gardeners consider it a weed [5].

3. Biochemical Compounds of *Melissa officinalis*

M. officinalis is widely used in food, medicine, and cosmetics. Its application is particularly related to the presence of valuable phytochemicals such as pleasant volatile compounds (e.g., Neral, geranial, citronellal), phenolic acids (e.g., rosmarinic acid), flavonoids (e.g., luteolin) and many others (Fig. 1). In 1998, Carnat and co-authors have

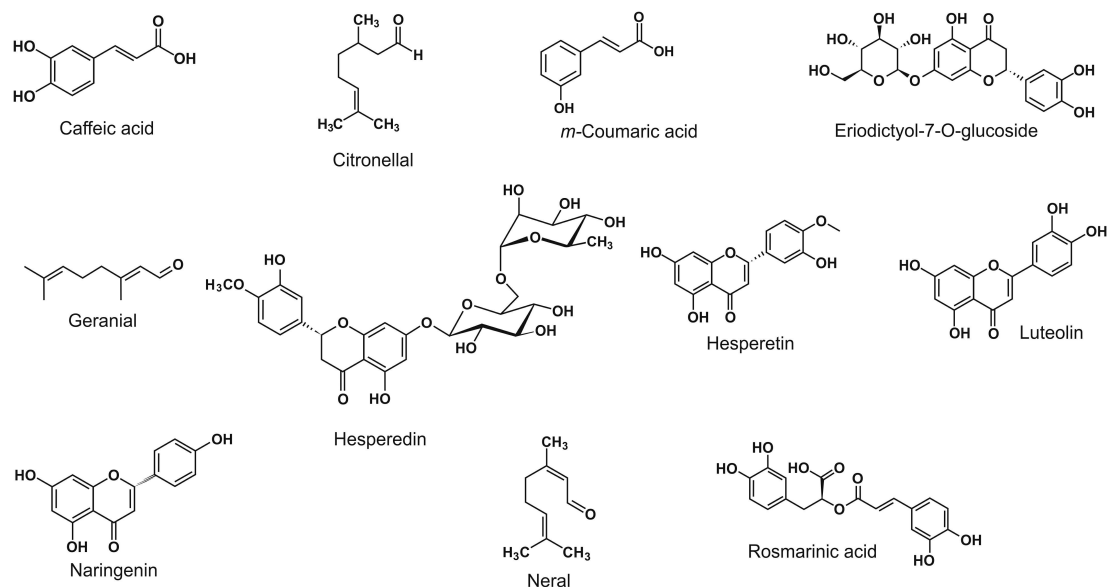


Fig. 1. Chemical structure of the main phytochemicals of *M. officinalis* L.

reported that *M. officinalis* leaves contained 0.32% essential oil, 11.8% polyphenol compounds (hydroxycinnamic compounds 11.3%, RA 4.1%, and total flavonoid compounds 0.5%) [13]. Later, Shakeri and co-workers described that *M. officinalis* contained volatile compounds, triterpenoids, phenolic acids, and flavonoids [6].

3.1 Volatile Oils

The volatile compounds of *M. officinalis* have been intensively studied in many countries. The chemical composition of volatile oils of *M. officinalis* from different origins is represented in Table 1 (Ref. [2,14–25]). According to the literature reports, the major components of the *M. officinalis* essential oils are mono-, sesquiterpenes, and aliphatic aldehydes, alcohols such as geranial, neral, and citronellal, geranyl acetate, (*E*)-caryophyllene, caryophyllene oxide, geraniol, pinene, sabinene, thymol, carvacrol and muurolene, decadienal and *trans*-carveol [2,6,13–25]. The numerical cluster analysis has been carried out based on 15 major essential oil components from thirty *M. officinalis* samples published in the literature. Geranial/neral (I); geraniol/caryophyllene oxide (II); citronellal (III); α -pinene/caryophyllene oxide (IV) chemotypes have been reported for the essential oil compositions of *M. officinalis* [14].

3.2 Triterpenes

Several new triterpenes were discovered from *M. officinalis*. Mencherini and others have been isolated six new ursane-type triterpenes from the leaves and leaves of *M. officinalis* [26]. Recently, three new ursene triterpene glycosides (melissiosides A–C) with promising antimicrobial actions have been isolated from the aerial parts of *M. officinalis* [27]. In 2015, Ji and co-authors isolated serrata-

genic acid, $2\alpha,3\beta$ -dihydroxy-urs-12-en-28-oic acid, ursolic acid, oleanolic acid, $2\alpha,3\beta,23,29$ -tetrahydroxyolean-12-en-28-oic acid from *M. officinalis* leaves [28]. Ursolic and oleanolic acids were also detected in the methanol extract from dried aerial parts of lemon balm [29].

3.3 Phenolic Compounds

Hanganu and co-authors (2008) have reported that *M. officinalis* leaves contain 0.64% flavonoids expressed in rutoside and 8.962% phenyl-propane derivatives expressed in caffeic acid [30]. Six polyphenolic compounds, i.e., caftaric acid, caffeic acid, *p*-coumaric acid, ferulic acid, luteolin, and apigenin were identified from ethyl-ether, ethyl acetate, and 1-butanol extracts of *M. officinalis* leaves [30]. Toth and co-authors have reported that an important phenolic active compound of *M. officinalis* was RA [31]. In 2002, Patora and Klimek isolated for the first time a new glycoside compound, 7-O-beta-D-glucopyranoside-3'-O-beta-D-glucuronopyranoside from the leaves of *M. officinalis* [32]. In 2015, Ji and co-authors isolated thirteen compounds, including protocatechuyl aldehyde, vanillin, luteolin, rosmarinic acid, luteolin-7-O- β -D-glucopyranoside, luteolin 7-O-beta-D-glucuronopyranoside, luteolin 3'-O-beta-D-glucuronopyranoside and luteolin 7-O-beta-D-glucopyranoside-3'-O-beta-D-glucuronopyranoside have been isolated from the leaves of *M. officinalis* [32].

3.4 Others Compounds

β -Sitosterol and palmitic acid were isolated from the leaves of *M. officinalis* [28]. Aqueous *M. officinalis* preparations were rich in total phenols (2.9–7.8 mg/mL) and the examined macroelements, 4.4–11.6, 12.2–1152, and 200–

Table 1. Volatile compounds of *M. officinalis*.

Origin	Plant's part	Composition	References
Algeria	leaves	geranial (44.20%), neral (30.20%) and citronellal (6.30%)	[15]
Bulgaria	aerial parts	citronellal (18.5%), geraniol (15.2%), citronellol (9.5%), geranyl acetate (7.2%) and geranial (5.9%)	[16]
Egypt	aerial parts	geranial and neral (54.82%)	[17]
Greece	leaves	β -pinene (6.4–18.2%), sabinene (6.9–17.4%), (<i>E</i>)-caryophyllene (7.2–15.3%), caryophyllene oxide (12.6–24.4%)	[18]
Iran	flowers	trans-carveol (28.89%), citronellol (25.24%), δ -3-carene (5.26%), citronellal (4.9%), geraniol (2.2%), 1-octene-3-ol (2.03%) and spathulenol (2.06%)	[19]
Iran	aerial parts	geranyl acetate (27.9%), citral (24.2%), citronellal (8.4%), and citronellol (7.6%)	[2]
Iran	leaves	before flowering stage: decadienal (29.38%), geraniol (25.3%), caryophyllene oxide (8.75%), geranyl acetate (5.41%); in the flowering stage: decadienal (28.04%), geraniol (24.97%), caryophyllene oxide (7.55%), caryophyllene E (4.65%); and after flowering stage: carvacrol (37.62%), methyl citronellate (32.34%), geranyl acetate (5.82%), caryophyllene (5.50%)	[20]
Jordan	leaves	caryophyllene oxide (43.6%), muurolene (28.8%)	[21]
Poland	aerial parts	camphene, citronellal, neral, methyl citronellate, geranial, α -copaene, β -caryophyllene, humulene, caryophyllene oxide	[22]
Romania	aerial parts	citral (neral and geranial) (16.10%), citronellal (3.76%) and trans-caryophyllene (3.57%)	[23]
Russia	aerial parts	citronellol (36.71%), geraniol (27.20%)	[24]
Tajikistan	aerial parts	geranial (43.2%), neral (31.5%), (<i>E</i>)-anethole (12.3%), (<i>E</i>)-caryophyllene (4.0%) and citronellal (2.8%)	[14]
Turkey	aerial parts	citronellal (36.62–43.78%), citral (10.10–17.43%), thymol (0.40–11.94%), and β -caryophyllene (5.91–7.27%)	[25]

Melissa officinalis

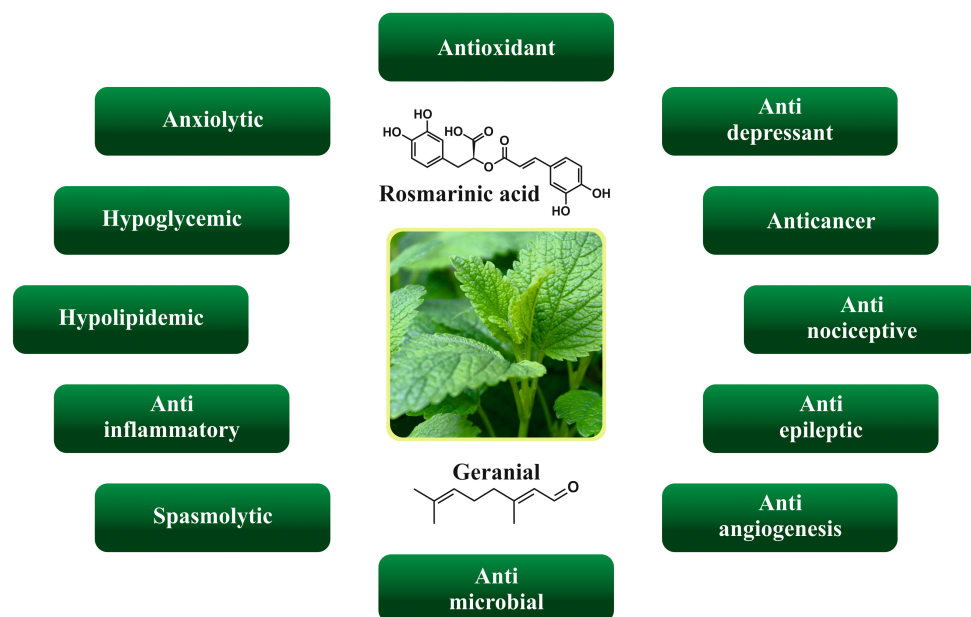


Fig. 2. Various health properties of the *Melissa officinalis*.

740 $\mu\text{g/mL}$ for Na, K, and Ca, respectively [33]. In summary, *M. officinalis* represents a promising source of phytochemicals that can contribute to the beneficial properties of the plant.

4. Health Properties of *Melissa officinalis*

The *Melissa officinalis* possess diverse biological and health properties such as anxiolytic, antioxidant, antidepressant, anticancer, antinociceptive, anti-epileptic, anti-

angiogenesis, antimicrobial, anti-inflammatory, hypolipidemic, and hypoglycemic. Various health properties of the *Melissa officinalis* are depicted in Fig. 2.

4.1 Antiviral Activity

COVID-19 has been defined as a pandemic on 11 March 2020 and entered the fifth position of the most important and documented pandemics since the 1918 influenza outbreak [34]. Worldwide researchers and clini-

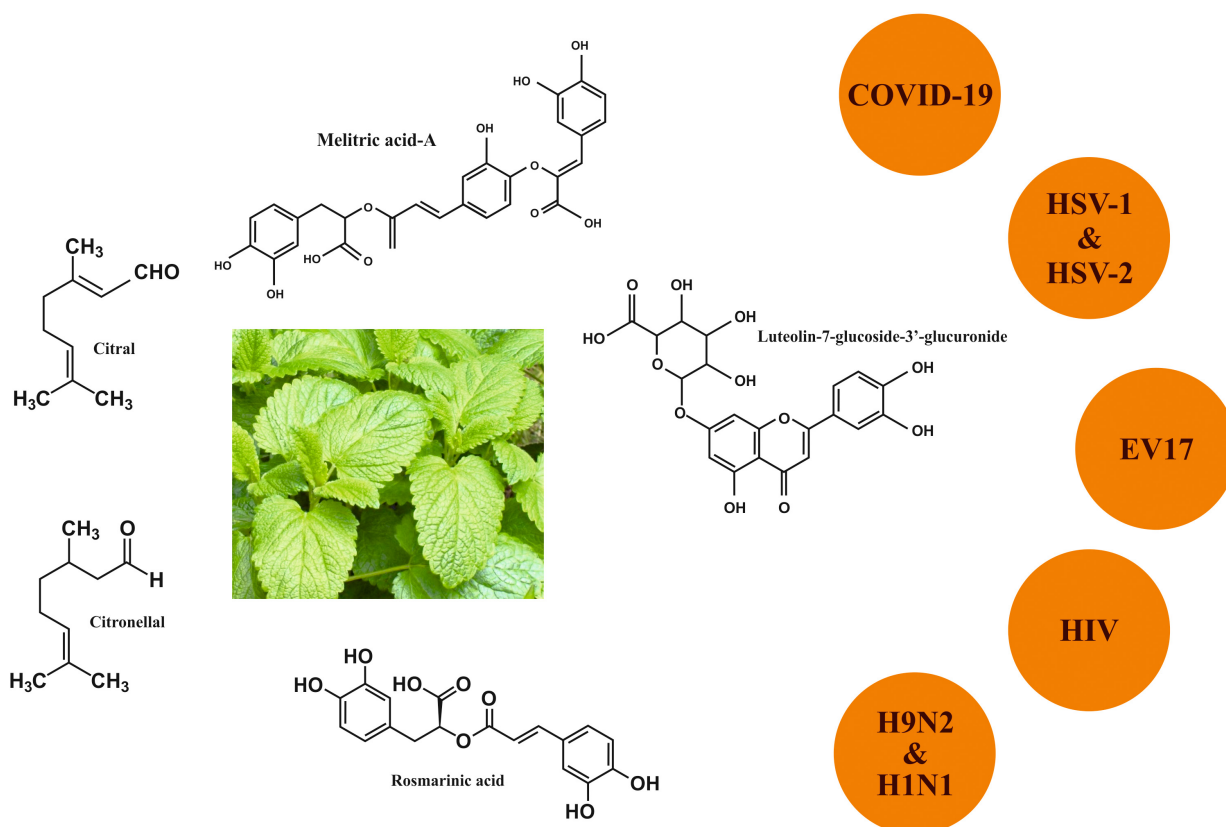


Fig. 3. Anti-viral activity of *Melissa officinalis* L.

cians hardly worked to find effective therapies and develop vaccines to reduce and prevent infectivity. Plants' bioactive compounds represent a major field of research for the development of safe and effective treatments potentially useful to fight against COVID-19. Several studies showed that *M. officinalis* possessed antiviral activity against a wide number of viruses (Fig. 3) [35]. Today's research aims to recognize its antiviral bioactive compounds against the main protease and spike protein of COVID-19. Docking experiments conducted by Prasanth and his colleagues showed that three phytoconstituents from *M. officinalis*, namely, luteolin-7-glucoside-3'-glucuronide, melitric acid-A, and quadranoside-III, possessed a greater binding affinity and stability towards the primary protease and spike protein of COVID-19 [36]. Similar results were previously published by Elekofehinti *et al.* [37] who found that melitric acid A and salvanolic acid A had higher affinity to the main protease of coronavirus COVID-19 than lopinavir and ivermectin using both AutodockVina and XP docking algorithms.

Influenza viruses that belong to a virus family known as Orthomyxoviridae are also a target of the active ingredients of *M. officinalis*. The H9N2 subtype virus, a member of the influenza family that has been classified as a low pathogenic virus, had unfortunately developed viral resistance to all the conventional drugs approved by the Food and Drug Administration (FDA) [38,39]. Recent findings

showed that *M. officinalis* essential oil (monoterpenaldehydes citral a, citral b) could inhibit influenza virus replication by different mechanisms of action such as masking the host cellular surface protein, intracellular steps, and direct virucidal effect by structural damage [40]. It was also demonstrated that the combination of *M. officinalis* essential oil with oseltamivir augmented the inhibitory effect of the antiviral drug particularly at very low concentration (0.005 mg/mL) [40]. Similar results on the effect of the hydroalcoholic extract of *M. officinalis* on the growth of influenza virus subtype H1N1 in the MDCK cell culture were demonstrated by Jalali *et al.* [41].

Antiviral activity of extracts from *M. officinalis* has also been described for herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) [42,43]. Astani *et al.* [44] evaluated the antiviral activity of *M. officinalis* extract by choosing active phenolic compounds against HSV-1 and investigating their mechanism of action. They found that both the aqueous *M. officinalis* extract and the phenolic molecules significantly decreased the infectivity of HSV-1 at the early stage of virus replication. This action was mainly due to the inhibition of herpes viral attachment caused by the predominant phenolic compound in *M. officinalis* extract RA at a concentration of 9.75 μ g/mL [44]. The plant extract revealed superior virucidal activity if compared to single compounds, probably imputable to multiple interactions of phytochemicals [45]. The hydroalcoholic extract of *M. of-*

ficinalis rich with RA (4.1% w/w) decreased the cytopathic effect of HSV-2 on Vero cells (ATCC CCL-81) at concentrations starting from 25 µg/mL with a maximum inhibiting effect (60%) obtained at a concentration of 0.5 mg/mL [21]. Allahverdiyev *et al.* [46] proved that the volatile oils obtained from *M. officinalis* at concentrations above 100 µg/mL reduced the proliferation of HSV-2. They suggested that this activity could be due to the citral and citronellal that characterizes the plant's volatile oil by inhibiting protein synthesis in virus cells [46].

Worldwide HIV in 2019 affected approximately 38 million people, mainly adults (36.2 million) and 1.8 million children (<15 years old) [47]. Advances in HIV pharmacotherapy produced the current antiretroviral therapy (HAART), which significantly contributed to prolonging survival and alleviating patients' suffering [47]. Nonetheless, side effects and drug resistance are two key factors to consider for the development of new antiviral to be potentially added to the current regimen. Geuenich *et al.* [48] proved that aqueous extracts from *M. officinalis* exhibited high and concentration-dependent activity against HIV-1 virions due to the augmentation of the virion's density before its surface engagement.

Enterovirus 71 (EV71) is one of the major pathogens causing Hand, foot, and mouth disease (HFMD) in infants and children aged under 5 [49]. A small proportion of EV71-infected patients develop severe complications that can lead to death which urge the progress toward novel drugs affecting patients' medical history [50]. It has been reported that *M. officinalis* extract (due to its high RA content) could block plaque formation and viral protein synthesis in EV71-infected cells, suggesting a cytopathic effect of this methanolic extract [51].

4.2 Antibacterial Activity

Generally, aromatic plants are rich in essential oils with significant antimicrobial properties. GC-MS analysis revealed that the chemical composition of the essential oils extracted from *M. officinalis* was citronellal (37.33%), thymol (11.96%), citral (10.10%), and β -caryophyllene (7.27%). According to the disk diffusion agar assay and micro-dilution method, strong antimicrobial effects of the oils against *Salmonella typhimorium*, *Escherichia coli*, *Listeria monocytogenes*, and *Staphylococcus aureus* were found [51]. Results also showed that *S. aureus* was the most sensitive bacteria with the lowest MIC value (0.12 mg/mL) [51].

E. coli ATCC 25922 and the multiresistant strain of *Shigella sonnei* IPH-MR exhibited high sensitivity to the essential oil of *M. officinalis* [52]. The petroleum ether extract of *M. officinalis* demonstrated varying inhibitory potencies against Gram-positive bacteria in particular *Staphylococcus aureus* and *Pseudomonas aeruginosa* with MICs ranging between 1.65 and 191.40 µg/mL, while no antibacterial effect was reported against *Escherichia coli* and *Kleb-*

siella pneumonia [53]. Similar results were recorded for the hydro-alcoholic extract of *M. officinalis* which showed interesting antibacterial activity against *S. aureus* and *Staphylococcus epidermidis*, while gram-negative bacteria such as *E. coli* were less involved [54].

Notably, essential oils revealed significant antifungal activity, even if not in all cases. Prominent was the low MIC and MFC of the essential oil of *M. officinalis* against *Trichophyton tonsurans* if compared to the reference drug bifonazole (antimycotic) [52]. Also, the crude petroleum ether extract and its derived fractions demonstrated remarkable antifungal activities against *Candida albicans*, *Candida krusei*, and *Candida glabrata* with MICs of 0.30–345.10 µg/mL [53].

4.3 Anti-inflammatory Effects

The anti-inflammatory activities of *M. officinalis* leaves were widely examined. Results showed that its essential oil possessed anti-inflammatory activities, supporting its traditional use in different diseases related to inflammation and pain [55]. Recent works proved that the extract of *M. officinalis* exerted anti-inflammatory and antinociceptive effects by interacting with muscarinic and nicotinic receptors and the L-arginine-nitric oxide pathway which were ascribable to RA, terpenoids, and flavonoids [56]. RA and flavonoids are known to block different enzymes involved in the inflammatory process, such as cyclooxygenase, lipooxygenase, and monooxygenase [57].

Due to these anti-inflammatory properties, the extract of *M. officinalis* proved to have good effects in relieving symptoms of atopic dermatitis [57]. The anti-inflammatory property of *M. officinalis* is depicted in Fig. 4. Ramanauskien *et al.* [58] investigated the effect of *M. officinalis* extract and its RA content on skin cells in normal conditions and under oxidative stress. The work on human keratinocyte cells showed that, in oxidative stress conditions, RA decreased intracellular ROS by about 28%, while enhancing cell viability by 10–24% (at a concentration of 0.25–0.5 mg/mL) and protecting cells from H₂O₂ damage [58].

Anti-inflammatory and antinociceptive effects of *M. officinalis* were investigated with the histamine- and carrageenan-induced paw edema tests in rats and mice. It was found that pretreatment with the aqueous extract of *M. officinalis* considerably lessened inflammagen-induced paw edema in rats and diminished the nociceptive response in mice [59].

Müzell and his colleagues assessed the anti-inflammatory activity of an aqueous extract of *M. officinalis* in hepatic and renal lesions caused by acetaminophen in animal models [60]. Even if not hepatoprotective, the extract demonstrated a nephroprotective activity against acetaminophen lesions and exhibited an anti-inflammatory effect on carrageenan-induced pleurisy [60].

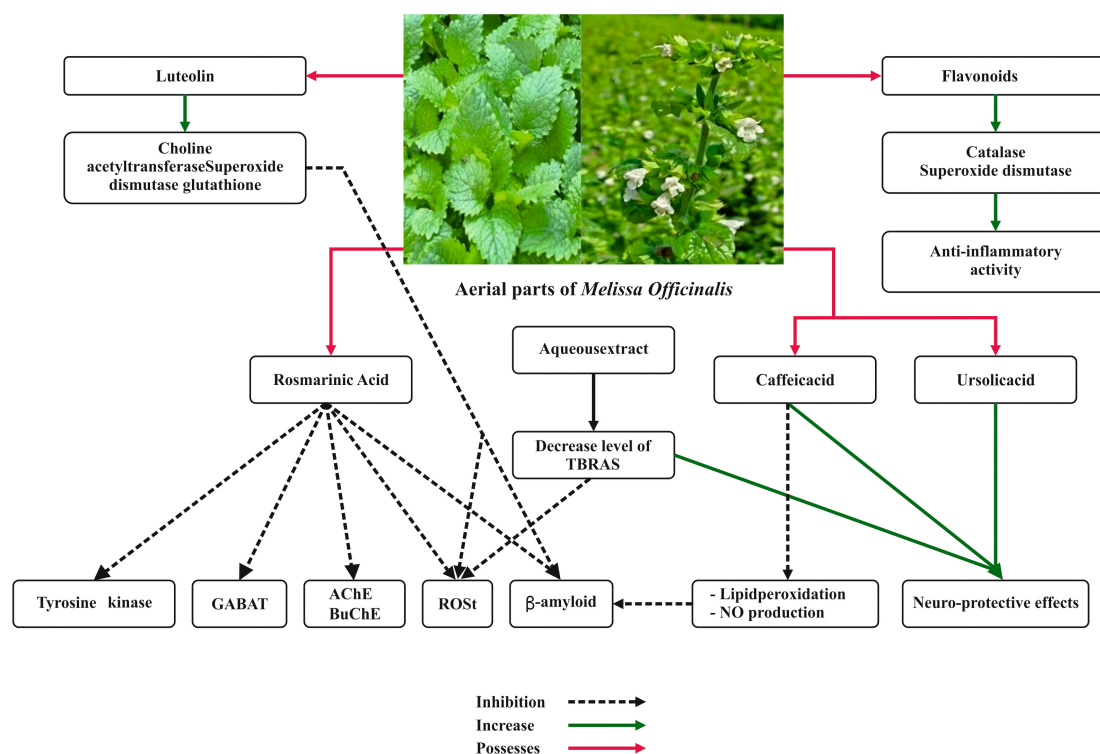


Fig. 4. Anti-inflammatory property and neuroprotective effects of *Melissa officinalis* L.

M. officinalis was also found to be a good source of chemopreventive agents. Its extracts demonstrated cytotoxicity in breast cancer cells (MDAMB- 231) even at low concentrations (100 $\mu\text{g/mL}$), with also a pronounced impact on cell migration and proliferation, while resulting in poorly toxic for HaCat cells (500 and 1000 $\mu\text{g/mL}$). Differently, stem extracts resulted highly cytotoxic (>100 $\mu\text{g/mL}$) [61].

4.4 Neuroprotective Properties

The number of people suffering from neurological disorders such as neurodegenerative diseases as well as psychiatric ones has lately increased worldwide [62]. *M. officinalis* has traditionally been used for its impact on the nervous system owing to elevated contents of phenolic compounds and tocopherols [52]. Both crude ethanol extract of *M. officinalis* and its fractions blocked acetylcholinesterase *in vitro* and *in vivo* [63–65]. Similarly, methanol and aqueous extracts of *M. officinalis* possessed a significant protective effect on hydrogen peroxide-induced toxicity in PC12 cells mainly due to monoamine oxidase inhibition [66]. In addition, the effects of an ethanol extract of *M. officinalis* were tested in the hippocampus of pilocarpine treated rats, as a potential model of epilepsy [67]. In particular, the antioxidative and anti-inflammatory activity of the extract orally administered at 250 mg/kg impacted positively on Nrf2/HO-1 signaling pathway, Na^+/K^+ -ATPase activity, and GABA while glutamate and acetylcholine diminished and reduced neuronal loss, adding a new potential beneficial effect (anti-epileptic) of *M. officinalis* to its wide uses.

Hassanzadeh *et al.* [68] reported that aqueous extract of *M. officinalis* could support neuroprotective effects against ecstasy-induced neurotoxicity in hippocampal primary culture. In addition, Yoo and his colleagues proved that oral administration of *M. officinalis* could augment differentiation and cell growth by lessening serum corticosterone while boosting GABA levels in the mouse dentate gyrus [69].

The effect of *M. officinalis* on hypoxia-induced neuronal death in a cortical neuronal culture system was tested both *in vitro* and in transient hippocampal ischemia *in vivo* models [70]. Cytotoxicity assays showed significant protection of *M. officinalis* against hypoxia in cultured neurons by decreasing caspase3 activity and TUNEL-positive cells significantly. *M. officinalis* oil was found to inhibit malondialdehyde levels and attenuate the decrease of the antioxidant capacity in the hippocampus. Pro-inflammatory cytokines TNF- α , IL-1 β , and HIF-1 α mRNA levels and HIF-1 α gene expression were highly decreased by the treatment with the plant [70]. Rosmarinic acid, the predominant compound of *M. officinalis*, demonstrated a cytotoxic effect on rat glioblastoma C6 cells by suppressing cell proliferation and inducing cell death through necrosis [71]. Extracts prepared with 70% ethanol were the most active on glioblastoma cells by initiating the generation of intracellular ROS and by inducing apoptosis and necrosis [71]. The pathophysiology of spinal cord injury (SCI) has a typically poor prognosis, that could lead to severe disabilities due to motor, sensory, and autonomic nervous system damage

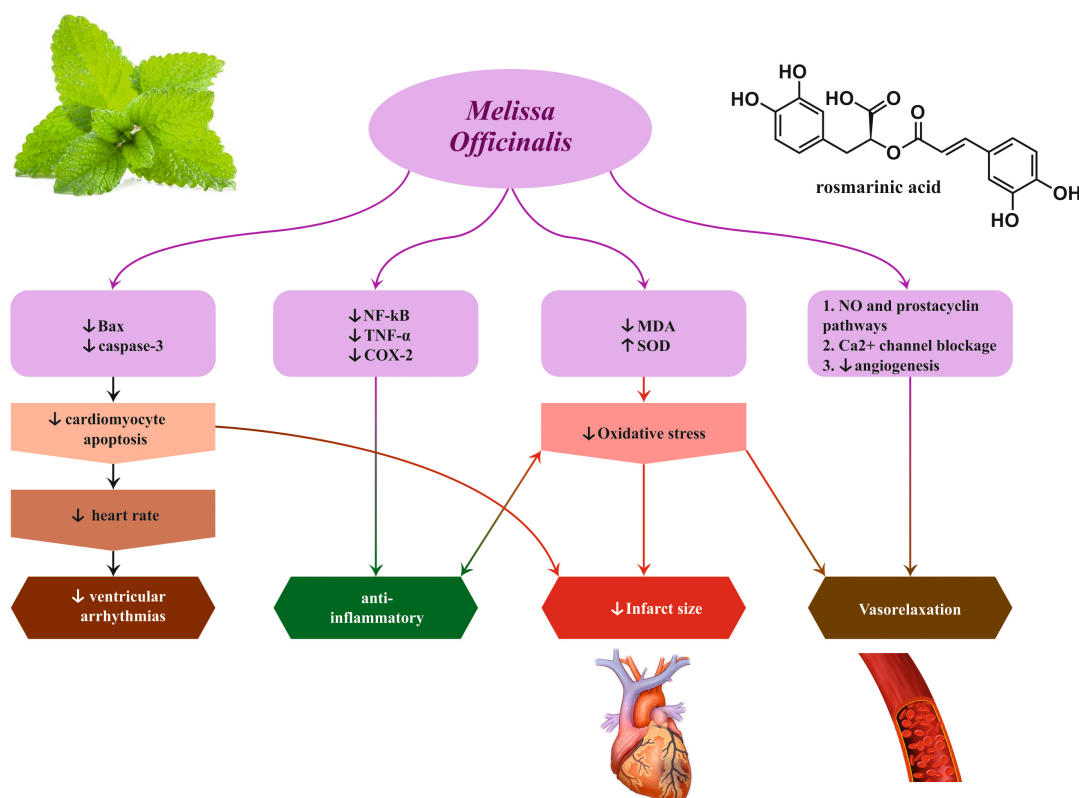


Fig. 5. Cardio-protective effects induced by *Melissa officinalis* L [78].

[72]. In a study conducted on adult male rats, Hosseini *et al.* [73] showed that human umbilical cord blood stem cells in combination with *M. officinalis* had neuroprotective effects in the SCI model. Researchers examined the behavioral mechanism of action of *M. officinalis* extracts on scopolamine-induced memory impairment in rats [64,74]. Although some studies showed that *M. officinalis* extract was completely inactive [74]; *M. officinalis* extract considerably improved scopolamine-induced learning deficit by enhancing the learning and memory of rats in other studies [64,74]. Results proved that *M. officinalis* extract reduced AChE mRNA level by 52% in the frontal cortex with a concomitant noteworthy blockade of BACE1 mRNA transcription [75]. More recently, *M. officinalis* oil 1 µg/mL was studied in isolated mouse ileum and atria tissues as a model of anxiety-related disorders [76]. The work reported that the oil could stop both spontaneous and induced ileum contractions, however, it reduced only slightly AChE activity, suggesting as other mechanisms (voltage-gated Ca^{2+} channels or muscarinic receptors) could be involved in *M. officinalis* effects.

5. Human Clinical Trials

M. officinalis extracts have been proved in clinical trials focused on a variety of diseases, mainly related to neurological disorders, i.e., anxiety and sleeping difficulties, but also metabolic problems and infantile colic. *M. officinalis* has been used as a cure for memory, cognition, anxiety, de-

pression, and heart palpitations for many centuries. Pre-clinical animal studies on this plant confirmed its evocative cardiovascular effects including anti arrhythmogenic, negative chronotropic and dromotropic, hypotensive, vasorelaxant, and infarct size-reducing, by the use of different extracts (aqueous, alcoholic, and hydroalcoholic), essential oil, or isolated compounds. Nonetheless, only the effectiveness of *M. officinalis* on heart palpitations has been verified in humans. Antioxidant free radical-scavenging properties, oxidative stress modulation, anti-inflammatory effects, activation of M2 receptors and antagonism of β_1 receptors in the heart, blockage of voltage-dependent Ca^{2+} channels, stimulation of endothelial nitric oxide synthesis, and prevention of fibrotic disease are the biological and biomolecular mechanisms suggested for the cardiovascular effects of *M. officinalis*. Furthermore, the principal active element of *M. officinalis* called rosmarinic acid has been demonstrated to have significant cardiovascular effects [7]. More recently, the same research group published a novel work on myocarditis using a rat model, suggesting the protective effects of this plant on cardiac function and related oxidative stress [77]. The cardio-protective effects induced by *M. officinalis* are depicted in Fig. 5 (Ref. [78]).

For the neurological effects, some authors investigated in the UK addressed the improvement of memory and brain function in healthy people by applying a combination of *Salvia officinalis* L., *Rosmarinus officinalis* L., and *M. officinalis* (SRM) [79]. The work showed that an

oral administration of *M. officinalis* combination at a dose of 5 mL twice a day for 2 weeks was more effective compared to placebo. Araj-Khodaei *et al.* [80] with a study on neurological disorders used *M. officinalis* to treat 45 adult outpatients who met the diagnosis (Diagnostic and Statistical Manual of Mental Disorders) for major depression, and were randomly assigned to 3 groups to daily receive either 2 g of *M. officinalis* or 2 g of *Lavandula angustifolia* Mill. or also fluoxetine (20 mg) and were assessed until 8 weeks [80]. Although the results were promising (usefulness of the extracts in moderate depression), the absence of a placebo group was relevant for the conclusion of the study, suggesting that more work is necessary to support the use of these plants to treat depression.

Other authors, researched neurological disorders [81]. An *M. officinalis* extract enriched in RA was tested in a randomized placebo-controlled double-blind 24-week trial by evaluating the safety and tolerability (primary endpoint) of RA (500 mg daily) and its clinical effects and disease-related biomarker changes (secondary endpoints). The group of patients (n = 23) was affected by mild dementia as a result of Alzheimer's disease (AD). The outcomes demonstrated that no difference in vital signs or physical and neurologic examination was perceived between the placebo and *M. officinalis* groups. In addition, no severe adverse effects were found while the cognitive function was not modified in both groups. The authors concluded that *M. officinalis* extract (500 mg of RA taken daily) was safe and well-tolerated for AD patients. Therefore, these data suggested that RA can impact AD neuropsychiatric symptoms and can stop the deterioration of AD patients' conditions. Even though these investigations have been recent, it should be noted that several studies on the effect of *M. officinalis* to treat neurological disorders were reported more than a decade ago. Burns *et al.* [82] carried out a randomized, double-blind, placebo-controlled trial to study the effect of *M. officinalis* oil against agitation in AD. However, aromatherapy with *M. officinalis* oil was not effective. Also, years before, Kennedy *et al.* [83] conducted a similar study. In this case, the authors analyzed the effects of *M. officinalis* on the modulation of mood and cognitive performance [83]. High doses of *M. officinalis* (1600 mg) could improve cognitive performance. Other researchers conducted a similar study focusing on the efficacy and safety of *M. officinalis* extract in mild to moderate AD patients [84]. The use of 60 drops per day demonstrated an improvement in cognitive function after 4 months of treatment.

Other researchers have reported that *M. officinalis* could impact anxiety or sleep disorders. Indeed *M. officinalis* leaves (*Melissa* capsule) were evaluated on anxiety and sleep quality in patients undergoing coronary artery bypass surgery [85]. Eighty patients were administered three times a day with an herbal drug (500 mg of *M. officinalis* leaves) or a placebo (500 mg of wheat starch). Forty-nine % of the patients reduced their anxiety levels at seven days

and 54% improved their sleep quality [85]. Other authors showed that *M. officinalis* essential oil was effective in reducing agitated behavior in the elderly affected or not by dementia [86]. The study was conducted in a nursing home recruiting 39 patients affected by dementia and 10 control patients (no dementia). Treatment was given for two weeks followed by a two-week washout period before starting subsequent treatment. The results of the study suggested that *M. officinalis* essential oil could effectively decrease anxiety, however in patients without dementia.

Tavares-Silva and collaborators proved the usefulness of *M. officinalis* and *Phytolacca americana* L. (syn. *Phytolacca decandra* L.) alone or in combination, in children affected by sleep bruxism [87]. Fifty-two children participated in this trial, where *M. officinalis* reduced sleep bruxism up to 30 days after treatment. Another research group also discovered the combination of *M. officinalis* and *Nepeta menthoides* Boiss. & Buhse in sleep disorder [88]. The trial evaluated 80 patients treated with the 1000 mg dose of *M. officinalis* plus 400 mg of *N. menthoides* or a placebo for four weeks. The study established that a combined regimen possessed a substantial activity against insomnia.

In other studies carried out in Iran and UK through randomized, double-blind, placebo-controlled trials, high response to the use of *M. officinalis* to treat anxiety was observed. In the study conducted by Alijaniha *et al.* [89] *M. officinalis* extract was tested against heart palpitation. Leaf extract of *M. officinalis* (500 mg two times per day up to 14 days) considerably lessened the incidence of anxiety and palpitation, while no side effect was reported. Similarly, in the UK, two studies were carried out on the use of *M. officinalis* for anxiety problems. In the first one, the effects of *M. officinalis* on laboratory-induced psychological stress were examined using a 600 mg dose of herbal extract. This dose decreased the negative mood effects of the defined intensity stressor simulation while augmenting the self-ratings of calmness [90]. In the other work, the anxiolytic effect of the herbal combination was assessed during laboratory-induced stress [91]. In this case doses of 80 mg of *M. officinalis* and 120 mg of *Valeriana officinalis* L. improved the negative effects of the defined intensity stressor simulation on ratings of anxiety. It is worth noting that another study tested the effects of "cyracos" (standardized extract of *M. officinalis*) in anxiety disorders and sleep disturbance [92]. Long-lasting administration of this extract cyracos (600 mg per day up to 15 days) diminished the stress-related effects, such as insomnia (42%), anxiety (18%), and anxiety-associated symptoms (15%).

However, the use of *M. officinalis* has not only been studied for neurological disorders or patients suffering from anxiety and stress. Some other studies were redirected to other problems. Darvish-Mofrad-Kashani and collaborators studied the response of *M. officinalis* in behavior modifications [93]. In this work, the efficacy and safety of *M.*

officinalis in improving hypoactive sexual desire disorder in 89 women were evaluated. The treatment doses were 500 mg per day of aqueous extract of *M. officinalis* or placebo. Results demonstrated that *M. officinalis* extract at 4 weeks significantly increased desire, arousal, lubrication, orgasm, satisfaction, and pain scores compared to placebo in hypoactive sexual desire disorder in women. Other investigations were conducted on the use of *M. officinalis* by diabetic patients or for the treatment of metabolic disorders. Nayebe *et al.* [94] described the potential effect of *M. officinalis* in diabetic patients (type 2). The work analyzed 37 dyslipidemic diabetic patients treated or not with 500 mg capsules per day for up to 3 months. *M. officinalis* could significantly reduce only serum triglyceride level, while no other metabolic alteration was noted if compared to the control group. Another group of researchers also tested the hydroalcoholic extract of *M. officinalis* in type 2 diabetic patients. The clinical trial was conducted with 62 patients treated with *M. officinalis* or placebo of 700 mg per day twice for 12 weeks. *M. officinalis* caused a substantial modulation in fasting blood sugar, glycated hemoglobin (HbA1c), and systolic blood pressure [95]. On the same line, *M. officinalis* were suggested to modify biomarkers of oxidative stress, inflammation, and lipid profile in patients with stable chronic angina [96]. Indeed, 80 patients participated in this clinical trial and were challenged with a dose of 3 g per day for 8 weeks. *M. officinalis* capsules significantly ameliorated the lipid profile, malondialdehyde (MDA), highly sensitive c-reactive protein (hs-CRP) and PNO1 in patients with stable chronic angina. More recently, *M. officinalis* was studied in systolic and diastolic blood pressures of 49 hypertensive patients, receiving 400 mg/d capsules of the extract for 4 weeks [97]. The plant was able to significantly reduce blood pressure (systolic and diastolic) up to the follow-up period of 10 weeks in this double-blind, controlled, randomized crossover study. Furthermore, a randomized, double-blind, placebo-controlled trial with supplementation of *M. officinalis* evaluated borderline hyperlipidemia patients [98]. Herbal capsules of *M. officinalis* exhibited interesting results in hyper-lipidemic patients, reducing low-density lipoprotein (LDL) and aspartate transaminase (AST) in patients treated with 500 mg of *M. officinalis*.

Finally, we must highlight the studies carried out with this plant to treat infantile colic. Martinelli *et al.* [99] demonstrated the effectiveness of *Matricaria chamomilla* L., *M. officinalis*, and *Lactobacillus acidophilus* tyndallized (HA122) in infantile colic. The children (n = 176) were treated for up to 28 days. Crying time was significantly shorter in the group that received *M. chamomilla*, *M. officinalis*, and *L. acidophilus* tyndallized than the group that received only *Lactobacillus reuteri* or simethicone. Similar to the previous work, another study investigated the effectiveness and side effects of *M. officinalis* associated or not with *Matricariae recutita* and *Foeniculum vulgare* in infantile

colic during one-week treatment. Again crying time was lessened in 85.4% of subjects compared to control (48.9%) while no side effects were reported [100].

The use of *M. officinalis* for various diseases, from neurological, metabolic disorders to infantile colic opens a new insight into scientifically supported treatments.

6. Toxicity

As for numerous plants, also *M. officinalis* can exert toxicity if not optimally used.

6.1 Cell-based Toxicity

An aqueous extract of *M. officinalis* exhibits showed low toxicity on RC-37 cells a cultured line derived from African green monkey kidneys, with a 50% cytotoxic concentration of 350 $\mu\text{g/mL}$ and a maximum non-cytotoxic concentration of 150 $\mu\text{g/mL}$ [101] and inhibited the proliferation of the NCI-H460 cells, with a growth inhibition 50% (GI_{50}) concentration of 200 $\mu\text{g/mL}$ [102]. *M. officinalis* hydroethanolic extract showed a cell viability of 13% at 1000 $\mu\text{g/mL}$ after 72 h on Human Colon Cancer Cell Line (HCT-116) [103] while its ethanolic inhibited the proliferation of the NCI-H460 cells, with a GI_{50} concentration of 100.9 $\mu\text{g/mL}$ [102]. *M. officinalis* decoctions and hot extract showed an antiproliferative effect on human tumor cell lines, with GI_{50} ranging from 51 to 258 $\mu\text{g/mL}$ for breast (MCF-7), non-small lung (NCI-H460), cervical (HeLa), and hepatocellular carcinoma (HepG2) [104] and at a concentration of 500–1000 $\mu\text{g/mL}$ for human colon cancer cell lines DLD-1 HCT116, SW620, HT-29, and inhibited HT-29 cells [105]. *M. officinalis* decoctions also showed hepatotoxicity activity with GI_{50} greater than 400 $\mu\text{g/mL}$ on fresh porcine liver cells, PLP2 [106]. *M. officinalis* volatile oil was non-toxic to HEP-2 cells, a human cervical carcinoma cell line at 100 $\mu\text{g/mL}$ [46] but induced a neurotoxicity effect on mixed cortical cell cultures from 16- to 18-day-old rat embryos (Sprague-Dawley strain) at the same concentration via volt aggregated sodium channels [106].

6.2 Animal-based Toxicity

M. officinalis leaves essential oil extract showed no acute toxicity in rats treated with 2000 mg/kg [30]. The oral administration of aerial parts essential oil of *M. officinalis* presents the oral LD50 in BALB/c mice (2.57 g/kg). This oil altered animal behavior and liver and kidney biochemical parameters at doses higher than 1 g/kg in BALB/c mice. Besides, an increased rate of lipid peroxidation and a depletion of antioxidant capacity of the liver and kidney suggest moderate toxicity [107]. *M. officinalis* whole methanolic and aqueous extracts were found to be safe or non-toxic to rats up to 2000 (mg/kg b.wt.) with no mortality in swiss albino mice [108]. This suggests that the organic extracts of *M. officinalis* are less toxic through the oral route than the essential oil extracts irrespective of the plant parts. In

addition, *M. officinalis* aqueous extract showed to cause genotoxic and histopathologic damage to the liver, kidneys, heart, and spleen if consumed by *Oncorhynchus mykiss* fish at doses greater than 450 mg/kg [109], while ethanolic extract showed no antigenotoxic/antimutagenic properties in Swiss albinos mice at 100–250 mg/kg [110]. However, the European Commission, the Panel on Additives and Products or Substances used in Animal Feed could not conclude on the safety of the use of a dried aqueous ethanol extract of *M. officinalis* leaves as a sensory feed additive for all animal species [111]. On the other hand, a randomized controlled trial using a single dose of *M. officinalis* extract comprising 500 mg rosmarinic acid, showed to be harmless and well tolerable in healthy humans [112]. This is confirmed by randomized clinical trials where different treatment regimens of *M. officinalis* extracts also showed no adverse effects in humans [84,94,95,113]. Overall, though *M. officinalis* toxicity data are scarce and have been poorly investigated despite the variety of practical applications in medical science, available data point out its putative safety in human beings.

7. Conclusions and Future Perspectives

M. officinalis is a medicinal plant with numerous health properties and is a curative tool for fighting cardiovascular, neurological, and psychological disorders. Nonetheless, *M. officinalis* is commonly known and prevalently used for anti-anxiety and anti-depression properties, particularly in the acute setting (among the general population *M. officinalis* is used to calm and relax). As reported in this work, this plant can be useful also in other human conditions, such as palpitation, hypertension, dementia, infantile colic, bruxism, metabolic problems, Alzheimer's disease, and sexual disorders. Even if the therapeutic effects of *M. officinalis* are well documented and studied, its current use in clinical settings is scarce and anecdotic. Thus this work wants to fill in this gap and suggest clinicians, general practitioners, physiotherapists, and interested people expand the rational use of this recognized curative plant. From a pharmacological point of view, *M. officinalis* possesses a wide number of remarkable properties, i.e., antiviral, anti-inflammatory, antibacterial, neuroprotective among the most common. In particular, antiviral activity is of current interest, because COVID-19 pandemic is still taking its toll and in the future, we will need new therapeutic tools to fight this disease, even in the perspective to co-exist with the SARS-CoV-2 virus. Moreover, given its safety — it is generally well tolerated having no relevant side effects, only occasionally headache, vomiting, abdominal pain, nausea have been reported — *M. officinalis* should be considered in general medicine to increase its use. Medicinal plants should be considered a powerful means to cure human conditions: this review sheds new light on the potential of *M. officinalis* and encourages researchers to increase the therapeutic possibilities of this medicinal plant.

Author Contributions

WZ, CQ, JSR, MDL, MS, MM, FS, PVTF, APM, DC, MK, JTC, RP contributed to the manuscript. WZ, CQ, JSR, MDL, MS, MM, FS, PVTF, APM, DC, MK, JTC, RP collected resources and were responsible for data curation and writing. Literature review analysis was performed by WZ, CQ, JSR, MDL, MS, MM, FS, PVTF, APM, DC, MK, JTC, RP. Reviewing and editing were carried out by JSR and RP. All the authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. JTC is serving as one of the Guest Editor of this journal. We declare that JTC had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GCA.

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