Advances in Bioresearch
Adv. Biores., Vol 15 (4) July 2024:280-290
©2024 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.4.280290

Advances in Bioresearch

REVIEW ARTICLE

Review on Lemon Balm Plant

Kiran. B. Andhale[1*] Mukesh. T. Mohite[b]
Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044
Corresponding Author: Kiran. B. Andhale
Email[1*]: kiranandhale1412@gmail.com

ABSTRACT
Biologically active chemicals abound in Lemon Balm, a medicinal plant recognized for its therapeutic properties around the world. The major ingredient in lemon balm is rosmarinic acid. Dry leaves of lemon balm contain 6% of rosmarinic acid. Lemon balm contains a high concentration of flavonoids, which may have anti-oxidant properties. It involves terpenes, tannins, eugenol, (+)-citronellal, 3-octanol, caffeic acid, caryophyllene, catechin, geranial, geraniol, iso-geranial and rosmarinic acid. Because of its anxiolytic, neuroprotective, hepatoprotective, and anti-inflammatory qualities, RA has been shown to have several positive health effects. Lemon balm is formally recommended for the therapy of mild anxiety problems. RA may be considered a good chemical in pharmacological development for treating depression. Melissa officinalis, sometimes recognized as lemon balm, has being utilized both historically and currently to modulate mood and cognitive function. When taken as capsules, coated tablets, or topically, lemon balm has been shown to have anxiolytic effects. These assessed the impact of a standardized plant formulation given in appetising forms such as yoghurt as well as beverage on mood and cognitive function. Lemon balm contains a high concentration of flavonoids, which may have antioxidant properties. Anxiolytic, neuroprotective, antidepressant, antidiabetic, antimicrobial, and antioxidant properties are all present in lemon balm.
Keywords: *Anxiolytic, Lemon balm, Melissa officinalis L, Rosmarinic Acid.*

Received 24.03.2024 Revised 01.04.2024 Accepted 30.06.2024

How to cite this article:
Kiran. B. Andhale, Mukesh. T. Mohite. Review on Lemon Balm Plant. Adv. Biores., Vol 15 (4) July 2024: 280-290.

INTRODUCTION

Due to all biologically active elements, lemon balm is a medicinal herb which is utilized all over the world for therapy. One of the medicinal herbs high in Rosmarinic Acid is lemon balm, with dry leaves with have up to 6% Rosmarinic Acid [1]. Because lemon balm has a host of physiologically active ingredients flavonoids, tannins, triterpenes, hydroxycinnamic acid derivatives, essential oil, and flavonoids—it has been utilized for millennia in traditional remedy in the direction of treating an array of illnesses [2]. The bulk of medications and nutraceuticals with lemon balm aim to treat insomnia or improve sleep. Lemon balm and its extracts' soothing and anxiolytic properties contribute with their most well-known health advantages [3-4]. In addition to food supplements, the European Union has designated set herbal constituents or extracts from the plant leaves as outmoded herbal medicinal yields for the management of mild gastrointestinal grievances such as swelling and pomposity, as well as the relief of mild mental stress symptoms and sleep aids [5]. To that aim, the European Pharmacopoeia requires that dried lemon balm leaves used in herbal medicines include at least 1% RA [6], whereas dry extracts derived from Melissa leaves must contain at least 2% RA [7]. Several health advantages exhibited by RA including anxiolytic, neuroprotective [8], hepatoprotective [9], and anti-inflammatory properties [10-11]. For instance, in human adipocytes, it causes adipocyte basal lipolysis [12] and inhibits several diabetes-related enzymes as well as white adipogenic development [13]. By lowering lipid peroxidation, and fibrosis severity, and generally enhancing liver biochemical markers, RA demonstrated hepatoprotective qualities [14]. Patients with osteoarthritis saw a considerable reduction in pain upon administration of extracts containing RA, owing to their potent anti-inflammatory activity. Along with other inflammation-related illnesses it also had an advantageous impact on skin inflammation and colitis such as atypical dermatitis [15-16]. Moreover, RA-containing extracts did not have any negative effects on the kidneys, liver, or other organs [17]. This is the reason that a lot of food supplements and preparations containing RA are sold

with promises about their health. Numerous studies show that RA is a more effective reactive oxygen species scavenger than artificial antioxidants like BHT and BHA [18]. It also exhibits strong pro-oxidant ion chelating capabilities and a greater lowering capability when compared to vitamin C [19]. Owing to its antibacterial characteristics and capacity to prevent lipid peroxidation, RA is being carefully studied for its possible application as a natural supernumerary for artificial antioxidants and preservatives in the food sector [20-21]. RA-containing extracts have been utilized to prolong the shelf life of bread [22], stabilize maize oil [23], and serve as a natural preservative in cupcakes [24] and non-alcoholic beverages. Additionally, RA had a substantial co-pigmentation effect on the anthocyanins in black chokeberries, hence enhancing their stability and intensity of colour [25]. Currently, in the European Union rosemary extract (E392) is the only plant extract containing RA that has been approved for use as a preservative in food [26].

Plant profile

Melissa officinalis plants in the Lamiaceae family grow bushy and straight, attainment a maximum height of 100 cm (39 inches). The 2- 8cm (0.79 to 3.50) long, heart-shaped leaves with a rough vein surface. They smell faintly like lemon and are hairy, velvety, and have scalloped edges. Little white or light pink flowers appear throughout the summer. Its citrus aroma is ideal when paired with aromatic teas. The perennial herbaceous plant known as lemon balm, a member of the mint family, is native to Iran, Central Asia, and south-central Europe, and has since spread throughout these regions. The herb was used by apothecaries, who supplied herbal cures directly to their clients, hence the second name, "officinalis." Lemon balm was brought to Great Britain by the Romans and quickly gained popularity as a plant for cottage gardens [27].

Historical use

The Plant belongs to mint family and originated in North Africa, Southern Europe, Western Asia and Mediterranean region. Now a day it is worldwide cultivated. It is utilized for the management of depression and sleep ailments. It may decrease anger and anxiety in new girls and women, and it can increase attention and energy levels. Typically, 20-50 g of dehydrated leaves is immersed in 1.0 L of heated water for 5-15 min. 3-4 cups of this tea are consumed every-day [27]. The necessary oil of plant, used in aromatherapy, is in charge for its therapeutic properties. However, phenolics, particularly RA, are similarly thought towards contribute in the direction of the healing capability of mentioned plant. Lemon balm has a modest essential oil level (0.02%-0.30%), compared to other Lamiaceae plants [27]. *Melissa officinalis* is a persistent grows that grows through a lemon fragrance. Lemon balm has been used therapeutically for over 2000 years. Paracelsus (1493-1541) suggested that described plant be used for "all complaints supposed to proceed from a disordered state of the nervous system" as well as that it could completely restore a man. This practice has been documented for over 2,000 years. Numerous herbalists have suggested that the plant has a wide range of beneficial benefits on the brain, including memory improvement. With anxiolytic effects after capsule, coated tablet, and topical application, it has been utilized in history. These assessed the impact of a standardized plants formulation given in appetising forms such as yoghurt and beverage on mood and cognitive function. The self-rated mood characteristics of a cohort of young adults in good health were assessed before and during the administration of a multi-tasking framework (MTF) 1-3 hours after 1 of 4 managements in each research.

Chemistry

High levels of flavonoids, which may have antioxidant effects, are present in lemon balm. It contains a combination of terpenes, tannins, and eugenol, as well as (+)-citronellal, 3-octanol, caffeic acid, caryophyllene, catechin, geranial, geraniol, iso-geranial, and rosmarinic acid. Vitamins B and C vitamins, Minerals: Iron, potassium, sodium, magnesium, and calcium. Potassium is beneficial to the heart of the active ingredients found in leaves; rosmarinic acid seems to be the most significant, containing 36.5 +/- 0.8 mg per gramme [27].

Therapeutic potential

Anxiolytic activity

33.7% of the population are affected by common mental illness including anxiety disorders. Remarkably, compared to the elderly population, young individuals have a higher prevalence of anxiety disorders. Despite notable advancements in the fields of psychotherapy and medication for anxiety disorders in recent times, anxiety disorders continue to have a large negative influence on society and come at a high cost. These factors make treating and preventing anxiety disorders the most important medical endeavour of the twenty-first century [28]. Tricyclic antidepressants, Benzodiazepines, Selective Serotonin Reuptake Inhibitors (SSRI), monoamine oxidase inhibitors are among the numerous medications available to treat anxiety disorders. Drugs were highly successful in treating anxiety problems when used. Nevertheless, according to certain investigations, there could be a wide range of

adverse consequences. The largest problem at the moment is that most people choose to neglect their mental illnesses and not seek help; this could be because of social stigma, a lack of general information, or a lack of understanding of available treatment options. As a result, symptoms linked to the body and/or the mind grew worse over time, resulting in longer hospital admissions and financial hardship. Given the social stigma associated with anxiety, patients find it much simpler to adopt alternative therapies like the use of ethnomedicinal. According to the findings of one of our earlier studies, over 40% of Serbian patients with various non-psychotic diseases treat their symptoms using various herbal medications. Melissa officinalis was listed as one of the most often used plant species. One common medicinal plant used to treat depression, anxiety, sleeplessness, anxiety-induced palpitations, and stress is lemon balm. Folk herbal medicine made from it is practiced in West Asia, the Mediterranean area, and central and southern Europe. It is noteworthy to add that Austrian folk has long utilized MO Essential Oil (MOEO) to cure a variety of illnesses, including those about the CNS. Clinical research on the CNS validated the taxon's pharmacological significance as well as the anxiolytic and neuroprotective properties of the MO extracts. Owing to the above-mentioned effects, MO is formally advised for the management of minor anxiety symptoms. The existence of rosmarinic acid has been linked to the plant's neurological effects, even if the key bioactive chemicals are yet unknown. Additionally, the extract of MO aerial portions contains a few additional water-soluble components such as metrilic acid, chlorogenic acid, and caffeic acids. Remarkably, at the time of the inquiry, there were very few papers addressing the anxiolytic effects of the volatile elements that make up the MOEO, according to a SciFinder search of the Chemical Abstracts Service (CAS) database [29].

Antidepressant activity

The effects of RA at dosages of 0, 3, 10, or 30 mg/kg were examined in female C57BL/6 mice sixty minutes previously injections of pentylenetetrazol (60 mg/kg). The dose effects of RA on mice were evaluated using rotarod, forced swim tests, novel item identification, and behaviour in the open environment. In the PTZ paradigm, RA enhanced comprehensive seizures as well as the inexpression towards myoclonic jerks in a dose-dependent routine as well as enhanced through pilocarpine. RA (30 mg/kg) improved the crossing quantity, the immobility duration, and the time spent in the open field's centre during the forced swim test [30]. Thus, RA may be viewed as an excellent molecule in pharmaceutical research for treating depression and causing modifications to BDNF stages and ERK11/2 signaling. In PC 12 cells, RA significantly improved cholinergic function and neurotrophic effects to the ERK1/2 signalling way as well as MAPK. Furthermore, pyruvate carboxylase (PC) and tyrosine hydroxylase (TH), which are convoluted in the regulation of serotonergic, GABAergic, as well as dopaminergic paths, were significantly up-regulated in response to RA. Moreover, TH shields neural cells from corticosterone's harmful effects [31].

Nephroprotective Action

Presently, the furthermost widely utilized antibacterial medications cause severe kidney impairment in 60% of attained contagions in hospitals through detectable morbidity rates [32]. Aminoglycosides are the ones that have been utilized the most to treat bacterial infections. Since it is less expensive and has a lower prevalence of antibiotic-acquired resistance, gentamicin is the most often used aminoglycoside; nonetheless, when administered therapeutically for longer than seven days at a dosage of 80 mg/kg/day, around 30% of patients have nephrotoxicity [33]. Acute renal toxicity is defined as the abrupt loss of kidney function caused by waste product accumulation, such as urea and creatinine. Since gentamicin-induced nephrotoxicity is associated with elevated levels of oxidative stress, this might play a major part in kidney injury [34]. Increased creatinine concentration and serum blood urea nitrogen in Sprague Dawley rats led to a decrease in myeloperoxidase and MDA levels. Actually, there were less event injuries in the group receiving RA. Moreover, RA dramatically reduced Bowman's capsule dilatation, tubular epithelium necrosis and dilatation, tubular epithelium degeneration, and localised glomerular necrosis [35]. Blood urea nitrogen and serum creatinine levels showed substantial upsurge due to RA at a dosage of 1, 2 and 5 mg/kg. Furthermore, RA reduced oxidative stress brought on by CP while increasing the expression of renal 4-hydroxynonenal, HO-1, and cytochrome P450 2E1 (CYP2E1). Furthermore, RA inhibited inflammation and decreased the expression of NF-κB and TNF-α. Moreover, RA reduced the expression of active caspase-3, phosphorylated p53, and p53 in the kidney by demonstrating an antiapoptotic effect [36]. RA dramatically decrease tubular necrosis, MDA, creatinine levels and urea in addition to markedly increasing renal SOD, GSH, GPS, CAT volume density PCT and creatinine clearance [37]. Finally, RA may provide defence against the neurotoxicity brought on by 6-hydroxydopamine because of its antioxidant properties [38].

Anti-diabetic Activity

RA sped up the rate of glucose rise, reduced serine IRS-1 phosphorylation, and accelerated the transfer of glucose by the glucose transporter type 4 (GLUT4) [39-40]. RA demonstrated a discernible hypoglycemic impact in rats caused by streptozotocin (STZ), whereas it enhanced insulin sensitivity in addition to enhanced glucose utilization in rats fed a more-fat diet (HFD). The effects due to HFD and STZ on GLUT4 expression in skeletal muscle as well as phosphoenolpyruvate carboxykinase expression in the liver were reversed by RA supplementation. In addition to improving production of hypoglycemic effect and insulin sensitivity, RA also decreases PEPCK expression and increases GLUT4 expression [41]. Furthermore, it prevents hyperglycaemia, improves cognition in healthy rat and strengthens the antioxidant defence system to restore memory and lipid peroxidation and learning deficits [42]. Rats with STZ-induced diabetes showed reduced levels of TBARS in their kidney and liver when treated RA at a dosage of 10 mg/kg. Its capacity to SOD activity as well as CAT was the primary factor in this result [43]. In diabetic rats, RA treatment also improved urine and water intake as well as oxidative stress indicators. It was therefore suggested that RA lessens the negative impact of free radicals on the tissues of rats, thereby mitigating the diabetes symptoms caused by STZ [44. Dose of 100 mg/kg, RA markedly enhance insulin index sensitivity and decreased levels of NF-κB, p-JNK, TNFα, IL-1β, HbA1c and blood glucose. Additionally, it dramatically lowered the levels of protein carbonyls, lipid peroxides, serum cholesterol, AOPPs, free fatty acids (FFA), and triglycerides in the pancreas and plasma of diabetic rats. The treatment of RA dramatically recovered the lowered actions of SOD, CAT, glutathione peroxidase and glutathione S-transferases as well as the abridged stages of vitamins E, C, GSH and ceruloplasmin in the plasma of diabetic rats [45-46]. Retinalactin moreover decreased the incidence of diabetes [47]. Treatment with RA dose of 10 mg/kg markedly decreased the amounts of lipid peroxidation in the diabetic rats' striatum (47%), cortex (38%), and hippocampal regions (28%) [48]. In STZ-induced diabetic Wistar rats, RA taken by mouth at 50 mg/kg for 10 weeks reduced endothelium-dependent relaxation along with upregulation of endothelin converting enzyme 1 and IL-1β, TNF-α, and preproendothelin-1 [49]. Additionally, it protects aortic endothelial function from damage brought on by diabetes [50].

Antimicrobial activity

Concerning RA's, it demonstrated antibacterial effects on strains of Staphylococcus aureus. The lowest blocking concentrations in contrast to *S. aureus* and MRSA were determined to be 0.8 and 10 mg/mL, respectively [51]. Conversely, the injection of RA exhibited a concentration- and time-dependent reduction in biofilm formation, indicating its potential utility as an efficient antibacterial agent for eliminating planktonic cell activity and lowering biofilm formation during the early stages of growth. By decreasing the number besides count of cells, RA similarly hinders the growing of Escherichia coli K-12 and Staphylococcus carnosus LTH150 [52]. RA interacted with nitrite ions in an acidic environment towards produce 6,6-nitro and 6-dinitrorosmarinic acids. Inhibiting viral replication in MT-4 cells, these substances acted as sub-molecular HIV-1 integrase inhibitors. The antiviral and anti-integrase inhibitory activities of RA nitration A were significantly enhanced without raising the levels of cellular toxicity [53]. Additionally, lactic acid bacteria, yeast, mould, Enterobacteriaceae species, Pseudomonas species, psychoactive counts, and Listeria monocytogenes inoculated in chicken foods were all susceptible to the antimicrobial actions of RA [54].

Antioxidant activity

Antioxidants are acknowledged for their noteworthy role in protecting against illnesses stemming from oxidative damage. ROS production might exceed a cell's antioxidant defenses, leading in the direction of oxidative stress. Crucially, it has been connected through DNA mutation, oxidation of proteins, and/or lipid peroxidation to the beginning and progression of several degenerative illnesses. It was discovered that *Melissa officinalis* L essential oils can be employed in foods that contain lipids and have a good potential for antioxidant activity. Antioxidants are abundant in it, especially those belonging to the phenolic chemical group. Its antioxidant properties resemble those of artificial antioxidants like BHA and BHT. Phenolic compounds such as citronellal and neral contribute in the direction of its antioxidant effects. The extracts' ability to inhibit lipid oxidation was evaluated by contrasting it with an extract from tea water. It revealed that there were many bound types of phenolic chemicals, counting flavonoids, hydroxycinnamic acids, caffeic acid and rosmarinic in the Melissa extract [55]. *The plant* presented substantial antioxidant action solitary in the polar fractions [56]. Antioxidant action and highest flavonoid content exhibited by ethyl acetate fraction [57]. Both artificial and natural free radicals can be scavenged by the lemon balm extract [58]. Melissa officinalis demonstrated a notable prevention of deoxyribose breakdown along with substantial reducing power [59]. In another investigation, DPPH, hydroxyl, and lipid peroxyl radical production were inhibited in a dose-dependent routine through H_2O extracts of Melissa officinalis L [60]. Melissa officinalis was established towards containing extremely higher

quantities of phenolics in 32 plant spices [61]. It had the maximum quantities of flavonoids and phenolics in another investigation [62]. Only four identified substances have been extracted from the desiccated stems and foliage of plant. Quadranoside III, luteolin, rosmarinic acid, and salvianic acid A were found as the known chemicals. The main component, rosmarinic acid, as well as the extracts' antibacterial and free radical-scavenging properties were assessed. The extracts of solid filtrates from supercritical extraction at 10 MPa, 323 K, and 30 min. had the highest value of phenol chemicals [63]. The phenolic profiles of various lemon balm samples were assessed. To comprehend the distinctions between commercial (bags and granulated) samples, in vitro cultured samples, and cultivated samples, the profiles were compared. The most prevalent component was rosmarinic acid [64-65].

Marketed product

Other tea mixes employ lemon balm as an herbal tea (Fig.4). Perfume is made with oil, and winemaking also uses flowers and leaves. Herbal liqueurs have traditionally included lemon balm as an ingredient.

Extraction of Lemon Balm

(Table 1) illustrated different method of extraction of lemon balm

Side effects

No adverse effects have been documented for the herb when applied externally or ingested at recommended dosages (up to 30 days) in generally healthy adults or when consumed in quantities typically found in food. This plant has been designated as Generally Recognized as Safe (GRAS) in the United States, with a permitted maximum level of 0.5% in baked goods. However, caution is advised regarding its use during pregnancy or breastfeeding, in children, or in individuals with thyroid issues, as well as when used concurrently with sedatives [66]. The plant extract possesses notable potential in promoting health and treating illnesses due to its volatile organic compounds and active ingredients like terpenoids, flavonoids, quercetin, rutin, quercitrin, gallic acid, and strong antioxidant properties. The essential oil extracted from the plant exhibited significant abilities to inhibit acetylcholinesterase and demonstrated antioxidant effects [55]. Additionally, the plant displayed noteworthy antioxidant properties specifically within its polar fractions. Within this plant, RA was identified as the predominant compound [64-65]. In the DPPH assay, comparisons between cultivated and in vitro cultured samples revealed the least concentrations of phenolic compounds in the former two, while commercial samples exhibited the highest levels [67]. Additionally, various studies, differing in quality, have indicated the radical scavenging and antioxidant capabilities of polar extracts derived from this plant [55]. These properties are attributed to the presence of flavonoids, RA, and benzodioxole. Notably, the antioxidant effects of these compounds are reported to be up to ten times more potent than those of vitamins B and C [64-65]. The findings of this investigation indicate that the majority of research into the therapeutic potential of this plant has been conducted through in vitro studies. Consequently, there is a pressing need for additional complementary studies to explore the diverse therapeutic effects of this plant through clinical trials. Despite existing research on antioxidant properties, further comprehensive examinations regarding toxicity and teratogenicity are warranted. Moreover, while there are various genera of this plant, each containing its distinct chemical compounds, many shares common compounds responsible for their antioxidant effects. Hence, further research is essential to identify new chemical compounds within untested genera of this plant that contribute to its antioxidant activity, ensuring safety within specified dosages [64-65].

DISCUSSION

The comprehensive analysis of lemon balm (*Melissa officinalis L.*) reveals its significant therapeutic potential and diverse pharmacological activities, primarily attributed to its major component, rosmarinic acid (RA). It has been traditionally utilized for periods in various regions of the world, owing to its wide array of biologically active compounds, including flavonoids, tannins, terpenes, and essential oils. The pharmacological activities of lemon balm encompass anxiolytic, neuroprotective, antidepressant, hepatoprotective, anti-inflammatory, anti-diabetic, antimicrobial, and antioxidant properties. These properties have been extensively studied and validated through numerous preclinical and clinical trials, providing robust evidence for its therapeutic efficacy across multiple health conditions. Anxiety disorders, affecting a significant portion of the population, have been a major focus of research, with lemon balm demonstrating promising anxiolytic effects comparable to conventional medications. Its ability to modulate mood and cognitive function has been well-documented, making it a valuable alternative therapy for individuals suffering from anxiety-related symptoms. Furthermore, lemon balm exhibits antidepressant activity, enhancing serotonin and dopamine levels, and modulating neurotropic factors involved in mood regulation. These effects highlight its potential as a natural remedy for depression and related mood disorders. In addition to its effects on mental health, lemon balm exerts

hepatoprotective effects, decreasing liver damage and inflammation, and enhancing liver function markers. This makes it a promising therapeutic agent for liver disorders and conditions associated with hepatic dysfunction. Moreover, lemon balm demonstrates significant anti-diabetic activity, improving insulin sensitivity, reducing blood glucose levels, and protecting against diabetes-induced oxidative stress as well as tissue impairment. Its antioxidant properties, recognized towards its higher sum of phenolic compounds, provide protection against oxidative impairment as well as played a critical part in preventing various degenerative diseases. The antimicrobial action of plant, particularly in contrast to bacterial and viral pathogens, underscores its potential as a natural antimicrobial agent for combating infections and promoting overall health. Overall, lemon balm emerges as a versatile medicinal plant with a wide range of therapeutic applications, supported by its rich phytochemical profile and pharmacological activities. Further research and clinical studies are warranted to elucidate its mechanisms of action, optimize dosage regimens, and explore its potential synergistic effects with conventional therapies, ultimately enhancing its efficacy and clinical utility in modern healthcare practice.

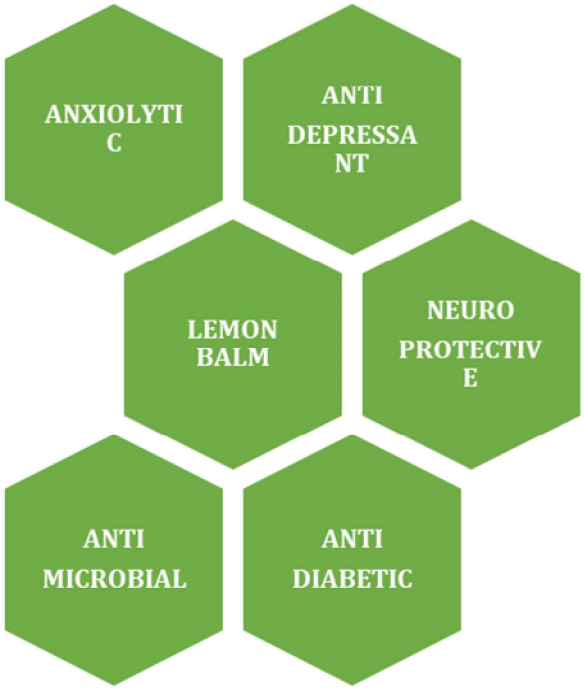

Fig.1: Application of plant

Fig.2: Lemon Balm Roots & Leaves

Fig.3: Lemon Balm Flower (28)

Fig.4: Lemon Balm Tea.

Table 1: Extraction of Lemon Balm

Temperature Assisted Dynamic Maceration	Static Maceration (SM)
1. In 100 mL screwcap Pyrex glass bottles, 4 g material was combined with 80 mL 50% (v/v) ethanol (a solid-to-liquid ratio of 1:20). 2. At 60°C, bottles were shaken for one hour in a water bath. 3. The extract was filtered once the bottles had cooled. 4. Temperature-Assisted Dynamic Maceration (TADM) extract was the result of two repetitions of the extraction process.	1. In brown glass flasks, 4 g of the powdered plant material and 80 mL of 50% (v/v) ethanol (solid-to-liquid ratio: 1:20) were combined for this operation. 2. For thirty days, flasks were kept at room temperature and manually shook each day. 3. 500 \L of the extracts were periodically removed for examination following centrifugation (6000 g, 20 min). 4. After two iterations of the extraction process, the extract was designated as SM extract. 5.Since the 10th day was when the maximum concentration of phenolic chemicals, including RA, was extracted, all data indicated with an SM solely relate to this sample

CONCLUSION

Melissa officinalis L. is rich in RA and other biologically active compounds, providing a wide array of therapeutic benefits. Its pharmacological activities include anxiolytic, neuroprotective, antidepressant, hepatoprotective, anti-inflammatory, antidiabetic, antimicrobial, and antioxidant properties. These effects have been validated through extensive research, making lemon balm a promising natural remedy for various health conditions. Its potential in treating anxiety, depression, liver disorders, diabetes, and

infections highlights its versatility in modern healthcare. Further studies are needed to fully understand its mechanisms and optimize its use in clinical practice.

ACKNOWLEDGEMENT
I would like to thanks my guide Mr. Mukesh Mohite for their guidance and support to complete this review work. I would also like to extend my thanks to the principal Dr. N S Vyawahare for providing me with all the facilities that were required.

AUTHOR CONTRIBUTION
Investigation, writing and editing is done by KBA. MTM is involved in designing of the article and RDK is involved in the review of data and improvement of the article.

CONFLICT OF INTEREST
The authors have no conflicts of interest.

REFERENCES
1. Verlag, G.T. (2nd Ed.) (2003). The Scientific Foundation for Herbal Medicinal Products. ESCOP Monographs, ESCOP: Stuttgart, Germany, Thieme, New York, NY, USA pp. 101.
2. Hänsel, R., Keller, K.; Rimpler, H.; Schneider, G.; (Eds.) 1993. Hagers Handbuch; Springer: Berlin/Heidelberg, Germany, pp. 1195. https://doi.org/10.1007/978-3-642-57881-6
3. Zhao, J., Xu, L., Jin, D., Xin, Y., Tian, L., Wang, T., Zhao, D., Wang, Z., & Wang, J. (2022). Rosmarinic Acid and Related Dietary Supplements: Potential Applications in the Prevention and Treatment of Cancer. Biomolecules, 12(10), 1410. https://doi.org/10.3390/biom12101410
4. Kwon, Y. O., Hong, J. T., & Oh, K.-W. (2017). Rosmarinic Acid Potentiates Pentobarbital-Induced Sleep Behaviors and Non-Rapid Eye Movement (NREM) Sleep through the Activation of GABA A -ergic Systems. Biomolecules & Therapeutics, 25(2), 105–111. https://doi.org/10.4062/biomolther.2016.035
5. European Medicine Agency, Committee on Herbal Medicinal Products (HMPC). Community Herbal Monograph on *Melissa officinalis* L., Folium, 196745/2012.2013. (Accessed on 5 February 2023). https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-melissa-officinalis-l-folium_en.pdf
6. Melissa Leaf. In Ph Eur Monograph 1447, European Pharmacopoeia, 7th ed.; Council of Europe, European Directorate for the Quality of Medicines and Healthcare: Strasbourg, France, 2013.
7. Melissa Leaf Dry Extract. In Ph Eur Monograph 2524, European Pharmacopoeia, 7th ed.; Council of Europe, European Directorate for the Quality of Medicines and Healthcare: Strasbourg, France, 2013.
8. Wang, S.-J., Chen, Q., Liu, M.-Y., Yu, H.-Y., Xu, J.-Q., Wu, J.-Q., Zhang, Y., & Wang, T. (2019). Regulation effects of rosemary (Rosmarinus officinalis Linn.) on hepatic lipid metabolism in OA induced NAFLD rats. Food & Function, 10(11), 7356–7365. https://doi.org/10.1039/C9FO01677E
9. Georgiev, M., Pastore, S., Lulli, D., Alipieva, K., Kostyuk, V., Potapovich, A., Panetta, M., & Korkina, L. (2012). Verbascum xanthophoeniceum-derived phenylethanoid glycosides are potent inhibitors of inflammatory chemokines in dormant and interferon-gamma-stimulated human keratinocytes. Journal of Ethnopharmacology, 144(3), 754–760. https://doi.org/10.1016/j.jep.2012.10.035
10. Zhao, L., Zhang, Y., Liu, G., Hao, S., Wang, C., & Wang, Y. (2018). Black rice anthocyanin-rich extract and rosmarinic acid, alone and in combination, protect against DSS-induced colitis in mice. Food & Function, 9(5), 2796–2808. https://doi.org/10.1039/C7FO01490B
11. Topal, M., & Gulcin, İ. (2022). Evaluation of the in vitro antioxidant, antidiabetic and anticholinergic properties of rosmarinic acid from rosemary (Rosmarinus officinalis L.). Biocatalysis and Agricultural Biotechnology, 43, 102417. https://doi.org/10.1016/j.bcab.2022.102417
12. Vasileva, L. V., Savova, M. S., Tews, D., Wabitsch, M., & Georgiev, M. I. (2021). Rosmarinic acid attenuates obesity and obesity-related inflammation in human adipocytes. Food and Chemical Toxicology, 149, 112002. https://doi.org/10.1016/j.fct.2021.112002
13. Elufioye, T. O., & Habtemariam, S. (2019). Hepatoprotective effects of rosmarinic acid: Insight into its mechanisms of action. Biomedicine & Pharmacotherapy, 112, 108600. https://doi.org/10.1016/ j.biopha. 2019.108600
14. Luo, C., Zou, L., Sun, H., Peng, J., Gao, C., Bao, L., Ji, R., Jin, Y., & Sun, S. (2020). A Review of the Anti-Inflammatory Effects of Rosmarinic Acid on Inflammatory Diseases. Frontiers in Pharmacology, 11. https://doi.org/ 10.3389/fphar.2020.00153
15. Stansbury, J. (2014). Rosmarinic Acid as a Novel Agent in the Treatment of Allergies and Asthma*. Journal of Restorative Medicine, 3(1), 121–126. https://doi.org/10.14200/jrm.2014.3.0109
16. Noguchi-Shinohara, M., Ono, K., Hamaguchi, T., Iwasa, K., Nagai, T., Kobayashi, S., Nakamura, H., & Yamada, M. (2015). Pharmacokinetics, Safety and Tolerability of Melissa officinalis Extract which Contained Rosmarinic Acid in Healthy Individuals: A Randomized Controlled Trial. PLOS ONE, 10(5), e0126422. https://doi.org/10.1371/journal.pone.0126422

17. Lagouri, V., & Nisteropoulou, E. (2009). Antioxidant Properties of O. Onites, T. Vulgaris and O. Basilicum Species Grown In Greece And Their Total Phenol And Rosmarinic Acid Content. Journal of Food Lipids, 16(4), 484–498. https://doi.org/10.1111/j.1745-4522.2009.01161.x
18. Cao, H., Cheng, W.-X., Li, C., Pan, X.-L., Xie, X.-G., & Li, T.-H. (2005). DFT study on the antioxidant activity of rosmarinic acid. Journal of Molecular Structure: THEOCHEM, 719(1–3), 177–183. https://doi.org/10.1016/j.theochem.2005.01.029
19. Amit, S. K., Uddin, Md. M., Rahman, R., Islam, S. M. R., & Khan, M. S. (2017). A review on mechanisms and commercial aspects of food preservation and processing. Agriculture & Food Security, 6(1), 51. https://doi.org/10.1186/s40066-017-0130-8
20. Vasileva, I., Denkova, R., Chochkov, R., Teneva, D., Denkova, Z., Dessev, T., Denev, P., & Slavov, A. (2018a). Effect of lavender (Lavandula angustifolia) and melissa (Melissa Officinalis) waste on quality and shelf life of bread. Food Chemistry, 253, 13–21. https://doi.org/10.1016/j.foodchem.2018.01.131
21. Vasileva, I., Denkova, R., Chochkov, R., Teneva, D., Denkova, Z., Dessev, T., Denev, P., & Slavov, A. (2018b). Effect of lavender (Lavandula angustifolia) and melissa (Melissa Officinalis) waste on quality and shelf life of bread. Food Chemistry, 253, 13–21. https://doi.org/10.1016/j.foodchem.2018.01.131
22. Vara, S., Karnena, M. K., & Dwarapureddi, B. K. (2019). Natural Preservatives for Nonalcoholic Beverages. In Preservatives and Preservation Approaches in Beverages (pp. 179–201). Elsevier. https://doi.org/10.1016/B978-0-12-816685-7.00006-9
23. Caleja, C., Barros, L., Barreira, J. C. M., Ciric, A., Sokovic, M., Calhelha, R. C., Beatriz, M., Oliveira, P. P., & Ferreira, I. C. F. R. (2018). Suitability of lemon balm (Melissa officinalis L.) extract rich in rosmarinic acid as a potential enhancer of functional properties in cupcakes. Food Chemistry, 250, 67–74. https://doi.org/10.1016/j.foodchem.2018.01.034
24. Klisurova, D., Petrova, I., Ognyanov, M., Georgiev, Y., Kratchanova, M., & Denev, P. (2019). Co-pigmentation of black chokeberry (Aronia melanocarpa) anthocyanins with phenolic co-pigments and herbal extracts. Food Chemistry, 279, 162–170. https://doi.org/10.1016/j.foodchem.2018.11.125
25. Carocho, M., Morales, P., & Ferreira, I. C. F. R. (n.d.). Natural food additives: Quo vadis?
26. Miraj, S., Rafieian-Kopaei, & Kiani, S. (2017a). 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
27. Kennedy, D., & Scholey, A. (2006). The Psychopharmacology of European Herbs with Cognition-Enhancing Properties. Current Pharmaceutical Design, 12(35), 4613–4623. https://doi.org/10.2174/ 13816 1206779010387
28. Atanasova, A., Petrova, A., Teneva, D., Ognyanov, M., Georgiev, Y., Nenov, N., & Denev, P. (2023). Subcritical Water Extraction of Rosmarinic Acid from Lemon Balm (Melissa officinalis L.) and Its Effect on Plant Cell Wall Constituents. Antioxidants, 12(4), 888. https://doi.org/10.3390/antiox12040888
29. Grigoletto, J., Oliveira, C. V. de, Grauncke, A. C. B., Souza, T. L. de, Souto, N. S., Freitas, M. L. de, Furian, A. F., Santos, A. R. S., & Oliveira, M. S. (2016). Rosmarinic acid is anticonvulsant against seizures induced by pentylenetetrazol and pilocarpine in mice. Epilepsy & Behavior, 62, 27–34. https://doi.org/10.1016/j.yebeh.2016.06.037
30. Jin, X., Liu, P., Yang, F., Zhang, Y., & Miao, D. (2013). Rosmarinic Acid Ameliorates Depressive-Like Behaviors in a Rat Model of CUS and Up-Regulates BDNF Levels in the Hippocampus and Hippocampal-Derived Astrocytes. Neurochemical Research, 38(9), 1828–1837. https://doi.org/10.1007/s11064-013-1088-y
31. Dashti-Khavidaki, S., Moghaddas, A., Heydari, B., Khalili, H., Lessan-Pezeshki, M., & Lessan-Pezeshki, M. (2013). Statins Against Drug-Induced Nephrotoxicity. Journal of Pharmacy & Pharmaceutical Sciences, 16(4), 588. https://doi.org/10.18433/J3T30F
32. Balakumar, P., Rohilla, A., & Thangathirupathi, A. (2010). Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to blunt it? Pharmacological Research, 62(3), 179–186. https://doi.org/10.1016/ j.phrs.2010.04.004.
33. Kang, C., Lee, H., Hah, D.-Y., Heo, J. H., Kim, C. H., Kim, E., & Kim, J. S. (2013). Protective Effects of Houttuynia cordata Thunb. on Gentamicin-induced Oxidative Stress and Nephrotoxicity in Rats. Toxicological Research, 29(1), 61–67. https://doi.org/10.5487/TR.2013.29.1.061
34. Ozturk, H., Ozturk, H., Terzi, E. H., Ozgen, U., Duran, A., & Uygun, I. (2014). Protective effects of rosmarinic acid against renal ischaemia/reperfusion injury in rats. JPMA. The Journal of the Pakistan Medical Association, 64(3), 260–265.
35. Domitrović, R., Potočnjak, I., Crnčević-Orlić, Ž., & Škoda, M. (2014). Nephroprotective activities of rosmarinic acid against cisplatin-induced kidney injury in mice. Food and Chemical Toxicology, 66, 321–328. https://doi.org/10.1016/j.fct.2014.02.002
36. Tavafi, M., & Ahmadvand, H. (2011). Effect of rosmarinic acid on inhibition of gentamicin induced nephrotoxicity in rats. Tissue and Cell, 43(6), 392–397. https://doi.org/10.1016/j.tice.2011.09.001
37. Ren, P., Jiang, H., Li, R., Wang, J., Song, N., Xu, H.-M., & Xie, J.-X. (2009). Rosmarinic Acid Inhibits 6-OHDA-induced Neurotoxicity by Anti-oxidation in MES23.5 Cells. Journal of Molecular Neuroscience, 39(1–2), 220–225. https://doi.org/10.1007/s12031-009-9182-y
38. Jayanthy, G., Roshana Devi, V., Ilango, K., & Subramanian, S. P. (2017). Rosmarinic Acid Mediates Mitochondrial Biogenesis in Insulin Resistant Skeletal Muscle Through Activation of AMPK. Journal of Cellular Biochemistry, 118(7), 1839–1848. https://doi.org/10.1002/jcb.25869

39. Inui, A., Cheng, K.-C., Asakawa, A., Amitani, H., Amitani, M., Morinaga, A., Takimoto, Y., Kairupan, B. H. R., & Runtuwene, J. (2016a). Rosmarinic acid ameliorates hyperglycemia and insulin sensitivity in diabetic rats, potentially by modulating the expression of PEPCK and GLUT4. Drug Design, Development and Therapy, Volume 10, 2193–2202. https://doi.org/10.2147/DDDT.S108539
40. Inui, A., Cheng, K.-C., Asakawa, A., Amitani, H., Amitani, M., Morinaga, A., Takimoto, Y., Kairupan, B. H. R., & Runtuwene, J. (2016b). Rosmarinic acid ameliorates hyperglycemia and insulin sensitivity in diabetic rats, potentially by modulating the expression of PEPCK and GLUT4. Drug Design, Development and Therapy, Volume 10, 2193–2202. https://doi.org/10.2147/DDDT.S108539
41. Hasanein, P., Felehgari, Z., & Emamjomeh, A. (2016). Preventive effects of Salvia officinalis L. against learning and memory deficit induced by diabetes in rats: Possible hypoglycaemic and antioxidant mechanisms. Neuroscience Letters, 622, 72–77. https://doi.org/10.1016/j.neulet.2016.04.045
42. Mushtaq, N., Schmatz, R., Ahmed, M., Pereira, L. B., da Costa, P., Reichert, K. P., Dalenogare, D., Pelinson, L. P., Vieira, J. M., Stefanello, N., de Oliveira, L. S., Mulinacci, N., Bellumori, M., Morsch, V. M., & Schetinger, M. R. (2015). Protective effect of rosmarinic acid against oxidative stress biomarkers in liver and kidney of strepotozotocin-induced diabetic rats. Journal of Physiology and Biochemistry, 71(4), 743–751. https://doi.org /10.1007/s13105-015-0438-4
43. Sotnikova, R., Kaprinay, B., & Navarova, J. (2015). Rosmarinic acid mitigates signs of systemic oxidative stress in streptozotocin-induced diabetes in rats. General Physiology and Biophysics, 34(4), 449–452. https://doi.org/10.4149/gpb_2015025
44. Govindaraj, J., & Sorimuthu Pillai, S. (2015). Rosmarinic acid modulates the antioxidant status and protects pancreatic tissues from glucolipotoxicity mediated oxidative stress in high-fat diet: streptozotocin-induced diabetic rats. Molecular and Cellular Biochemistry, 404(1–2), 143–159. https://doi.org/10.1007/s11010-015-2374-6
45. Ou, J., Huang, J., Zhao, D., Du, B., & Wang, M. (2018). Protective effect of rosmarinic acid and carnosic acid against streptozotocin-induced oxidation, glycation, inflammation and microbiota imbalance in diabetic rats. Food & Function, 9(2), 851–860. https://doi.org/10.1039/C7FO01508A
46. Vujicic, M., Nikolic, I., Kontogianni, V. G., Saksida, T., Charisiadis, P., Orescanin-Dusic, Z., Blagojevic, D., Stosic-Grujicic, S., Tzakos, A. G., & Stojanovic, I. (2015). Methanolic extract of Origanum vulgare ameliorates type 1 diabetes through antioxidant, anti-inflammatory and anti-apoptotic activity. British Journal of Nutrition, 113(5), 770–782. https://doi.org/10.1017/S0007114514004048
47. Mushtaq, N., Schmatz, R., Pereira, L. B., Ahmad, M., Stefanello, N., Vieira, J. M., Abdalla, F., Rodrigues, M. V., Baldissarelli, J., Pelinson, L. P., Dalenogare, D. P., Reichert, K. P., Dutra, E. M., Mulinacci, N., Innocenti, M., Bellumori, M., Morsch, V. M., & Schetinger, M. R. (2014). Rosmarinic acid prevents lipid peroxidation and increase in acetylcholinesterase activity in brain of streptozotocin-induced diabetic rats. Cell Biochemistry and Function, 32(3), 287–293. https://doi.org/10.1002/cbf.3014
48. Sotnikova, R., Okruhlicova, L., Vlkovicova, J., Navarova, J., Gajdacova, B., Pivackova, L., Fialova, S., & Krenek, P. (2013). Rosmarinic acid administration attenuates diabetes-induced vascular dysfunction of the rat aorta. Journal of Pharmacy and Pharmacology, 65(5), 713–723. https://doi.org/10.1111/jphp.12037
49. Azevedo, M. F., Lima, C. F., Fernandes-Ferreira, M., Almeida, M. J., Wilson, J. M., & Pereira-Wilson, C. (2011). Rosmarinic acid, major phenolic constituent of Greek sage herbal tea, modulates rat intestinal SGLT1 levels with effects on blood glucose. Molecular Nutrition & Food Research, 55(S1). https://doi.org /10.1002/ mnfr.201000472
50. Ekambaram, S., Perumal, S., Balakrishnan, A., Marappan, N., Gajendran, S., & Viswanathan, V. (2016). Antibacterial synergy between Rosmarinic acid and antibiotics against Methicillin resistant Staphylococcus aureus. Journal of Intercultural Ethnopharmacology, 5(4), 358. https://doi.org/10.5455/jice.20160906035020
51. Slobodníková, L., Fialová, S., Hupková, H., & Grancai, D. (2013). Rosmarinic acid interaction with planktonic and biofilm Staphylococcus aureus. Natural Product Communications, 8(12), 1747–1750. https://pubmed.ncbi.nlm.nih.gov/24555289
52. Dubois, M., Bailly, F., Mbemba, G., Mouscadet, J.-F., Debyser, Z., Witvrouw, M., & Cotelle, P. (2008). Reaction of Rosmarinic Acid with Nitrite Ions in Acidic Conditions: Discovery of Nitro- and Dinitrorosmarinic Acids as New Anti-HIV-1 Agents. Journal of Medicinal Chemistry, 51(8), 2575–2579. https://doi.org/10.1021/jm7011134
53. Raeisi, M., Tabaraei, A., Hashemi, M., & Behnampour, N. (2016). Effect of sodium alginate coating incorporated with nisin, *Cinnamomum zeylanicum* , and rosemary essential oils on microbial quality of chicken meat and fate of Listeria monocytogenes during refrigeration. International Journal of Food Microbiology, 238, 139–145. https://doi.org/10.1016/j.ijfoodmicro.2016.08.042
54. Meftahizade, H., Sargsyan, E., & Moradkhani, H. (2009). Investigation of antioxidant capacity of Melissa officinalis L. essential oils. Journal of Medicinal Plants Research. Journal of Medicinal Plant Research. 4(14), 1391-1395. 10.5897/JMPR10.148
55. Ferreira, A., Proença, C., Serralheiro, M. L. M., & Araújo, M. E. M. (2006). The in vitro screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from Portugal. Journal of Ethnopharmacology, 108(1), 31–37. https://doi.org/10.1016/j.jep.2006.04.010
56. Pereira, R. P., Boligon, A. A., Appel, A. S., Fachinetto, R., Ceron, C. S., Tanus-Santos, J. E., Athayde, M. L., & Rocha, J. B. T. (2014). Chemical composition, antioxidant and anticholinesterase activity of Melissa officinalis. Industrial Crops and Products, 53, 34–45. https://doi.org/10.1016/j.indcrop.2013.12.007

57. Dastmalchi, K., Damien Dorman, H. J., 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
58. Kamdem, J. P., Adeniran, A., Boligon, A. A., Klimaczewski, C. V., Elekofehinti, O. O., Hassan, W., Ibrahim, M., Waczuk, E. P., Meinerz, D. F., & Athayde, M. L. (2013). Antioxidant activity, genotoxicity and cytotoxicity evaluation of lemon balm (Melissa officinalis L.) ethanolic extract: Its potential role in neuroprotection. Industrial Crops and Products, 51, 26–34. https://doi.org/10.1016/j.indcrop.2013.08.056
59. Čanadanović-Brunet, J., Ćetković, G., Djilas, S., Tumbas, V., Bogdanović, G., Mandić, A., Markov, S., Cvetković, D., & Čanadanović, V. (2008). Radical Scavenging, Antibacterial, and Antiproliferative Activities of Melissa officinalis L. Extracts. Journal of Medicinal Food, 11(1), 133–143. https://doi.org/10.1089/jmf.2007.580
60. Wojdylo, A., Oszmianski, J., & Czemerys, R. (2007). Antioxidant activity and phenolic compounds in 32 selected herbs. Food Chemistry, 105(3), 940–949. https://doi.org/10.1016/j.foodchem.2007.04.038
61. Dias, M. I., Barros, L., Sousa, M. J., & Ferreira, I. C. F. R. (2012). Systematic comparison of nutraceuticals and antioxidant potential of cultivated, in vitro cultured and commercial Melissa officinalis samples. Food and Chemical Toxicology, 50(6), 1866–1873. https://doi.org/10.1016/j.fct.2012.03.057
62. Mencherini, T., Picerno, P., Scesa, C., & Aquino, R. (2007). Triterpene, Antioxidant, and Antimicrobial Compounds from Melissa officinalis. Journal of Natural Products, 70(12), 1889–1894. https://doi.org/10.1021/np070351s
63. Barros, L., Dueñas, M., Dias, M. I., Sousa, M. J., Santos-Buelga, C., & Ferreira, I. C. F. R. (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
64. Miraj, S., Rafieian-Kopaei, & Kiani, S. (2017a). *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
65. Ulbricht, C., Brendler, T., Gruenwald, J., Kligler, B., Keifer, D., Abrams, T. R., Woods, J., Boon, H., Kirkwood, C. D., Hackman, D. A., Basch, E., Lafferty, H. J., & Natural Standard Research Collaboration. (2005). Lemon balm (Melissa officinalis L.): an evidence-based systematic review by the Natural Standard Research Collaboration. Journal of Herbal Pharmacotherapy, 5(4), 71–114. https://pubmed.ncbi.nlm.nih.gov/16635970
66. Sofowora, A., Ogunbodede, E., & Onayade, A. (2013). The role and place of medicinal plants in the strategies for disease prevention. African Journal of Traditional, Complementary and Alternative Medicines, 10(5). https://doi.org/10.4314/ajtcam.v10i5.