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Melissa Officinalis: A Review on the Antioxidant, Anxiolytic, and Anti-depressant Activity

Lipoksenla[1], Viswedenu Kera[1], Sunit Nath[1], Avolu Kotso[1], Vekutolu Resuh[1], Abhijit Dutta[2] and Wankupar Wankhar[3]*

[1]Department of Medical Laboratory Technology, Faculty of Paramedical Science, Assam Downtown University, Panikhaiti, Guwahati, Assam, India.
[2]Faculty of Physiotherapy and Rehabilitation, Assam Downtown University, Panikhaiti, Guwahati, Assam, India.
[3]Faculty of Paramedical Science, Assam Downtown University, Panikhaiti, Guwahati, Assam, India.

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Anxiety and depression are among the most prevalent neuropsychiatric disorders globally and significantly contribute to the healthcare burden. Various factors, like stressful events, family history, substance abuse, health issues, hormonal imbalances, inflammation, and reactive oxygen species (ROS) mediated oxidative stress. Although numerous medications are available, their efficacy may diminish over time or vary among individuals. Phytomedicine offers a promising approach, focusing on herbal remedies with multiple therapeutic modalities. Melissa Officinalis (MO), a member of the Lamiaceae family, contains flavonoids, terpenoids, tannins, and phenolic acids. Essential oils from MO have shown potential in alleviating anxiety, enhancing mood, inducing relaxation, serving as an antidote, acting as an antidepressant, aiding sleep, boosting memory, and improving headaches and insomnia. However, the precise mechanisms underlying its therapeutic effects remain unclear. According to our literature, Melissa Officinalis and its active constituents exert their effects through (i) Antioxidant activity to prevent free radical-mediated neuronal damage. (ii) Blocking GABA-Transminase (GABA-T) activity to increase inhibitory GABA concentrations (iii) Inhibit serotonin and norepinephrine reuptake to increase serotonergic and noradrenergic transmission (iv) mild inhibition of Monoamine oxidase A MAO-A to prevent the deamination of amines. To promote the use complementary and alternative medicine by targeting multiple therapeutic modalities are reviewed in this study.

Keywords: Anxiety; Antioxidant; Depression; GABA; Melissa officinalis; Rosmarinic Acid.

Melissa Officinalis (MO), is commonly known as Lemon balm or mint balm [1-2]. Dioscorides (40 – 90 CE), the author of pharmaceutical wisdom, reported the remedial benefits of MO in his monumental work, " De Materia Medica." Historically, MO has had a wide range of medicinal uses in India, and it is now extensively used in the medicinal, nutritive, and aseptic sectors. [3]. *Melissa officinalis* is an edible herb native to the Middle East, Central Asia, and Iran and is a member of the Lamiaceae (mint) family [4]. It can also be found in the temperate zones of Kashmir, Uttarakhand, and other regions of southern India. The height of MO ranges from less than 8 inches to about 5

*Corresponding author E-mail: wankuparwankhar@gmail.com

feet. It is an erect herbaceous perennial with small, 2-lipped blooms with scalloped or tangled bunches of leaves with serrated edges that might be bright yellowish, white, pinkish, or, rarely, purple or blue. [5-6]. The plant is often utilised for its essential oils in the culinary, drug, beauty, and numerous pharmaceutical industries. [7]

Anxiety and depression

According to the Global Burden of Disease 2019 [8], the leading mental illnesses, anxiety and depression, contribute largely to the health care burden. The Global Health Data Exchange (GHDx) estimates that 970 million people worldwide, or approximately 1 in 80, were affected by chronic pain in 2019, with anxiety and depression being the most common. The COVID-19 outbreak has had a significant impact on internal health, such as depression and anxiety[9]. Depression and anxiety are not the same, and both conditions generally involve several of the same symptoms. Several theories like stressful events, family history, substance abuse, health problems, hormones, inflammation, ROS, antioxidant status, etc. can contribute to the pathogenesis of these disorders (Fig. 1). However, the neurochemical imbalance theories have caught the attention and are often linked to anxiety and depression [10]. To further supports the neurochemical imbalances theory, antidepressant, and anxiolytic drugs like SSRI (selective serotonin reuptake inhibitor) the first line of treatment, SNRI (Serotonin and Norepinephrine Reuptake Inhibitors), benzodiazepines, TCA (Tricyclic antidepressants), Monoamine oxidase inhibitors etc are constantly linked with regulating serotonergic, GABAnergic, glutamate, noradrenergic transmission, and monoamine oxidase. Nevertheless, the effectiveness of these drugs can vary among individuals and may decline or cease to operate as time passes. With the advancement of phytomedicine, targeting multiple therapeutic modalities may help alleviate this psychiatric illness.

***Melissa Officinalis* used by traditional practitioners**

Throughout the ages, different ethnic communities have used MO in treating hyperglycemic conditions, Alzheimer's disease, antidepressants, anxiolytics, painkillers, anti-inflammatory properties, spasmolytic actions, antioxidant, hypoglycemic, hypolipidemic, antimicrobial, antibacterial, and cytotoxic properties [11-17]. The essential oil in MO's leaves has been claimed to alleviate anxiety, enhance mood, promote a state of relaxation, work as an antidote, antidepressant, sleep aid, memory booster, and improve headaches, insomnia, irritability, and heart disease [18-19]. In addition, memory enhancement, menstruation induction, fever reduction, antimicrobial, spasmolytic, hypotensive, and endocrine system-related benefits were also reported [20]. They are also used in amenorrhoea, diarrhoea, mushroom toxicity, intestinal ulcers, guff, breathing difficulties, tumours, swellings, arthralgia, and toothaches [21].

Culinary use of *Melissa officinalis*

The essential oil of *Melissa officinalis* is used in food, herbal beverages, cosmetics, and home décor [22-23]. In the food industry, they are used as seasoning dishes, drinks, appetisers, meals, desserts, fruit salads, etc. [3, 24-25]. One of the most well-liked MO uses is tea, where the leaves are added to black, green, or Earl Grey tea [26]. The results of several studies have demonstrated that MO extracts' essential oils have the potential to be used as antioxidant supplements [27]. Scholey et al. [28] reported that individuals provided with 0.3g of the leaf extract mixed in a drink showed reduced anxiety symptoms. Similarly, blending with herbs like dill, tarragon, parsley, chervil, and chives can improve mental and cognitive health [24]. MO can be a wonderful substitute for green tea as it is efficient at lowering blood pressure, and weight, treating digestive, mental, hepatic, and biliary diseases, etc. [29-30]. With a permissible concentration of 0.5% in foods, MO is conferred GRAS (Generally Regarded as Secure) status in the US [31].

Phytochemistry of *Melissa officinalis*

Given its complex chemical constituents with a variety of therapeutic actions, the compounds extracted from MO have been intensively studied (Table:1). The essential oil of MO is extracted by chemically or steam distilling the plant's branches, flowers, and foliage, whether they are fresh or dried, to obtain its light-yellow colour and citrus scent. The fundamental chemical makeup of MO consists of phenolic substances (caffeic acid, rosmarinic acid, protocatechuic acid), flavonoids (luteolin, quercetin, and rhamnocitrin), and triterpenes (geraniol, neral, citronellal, geranial, oleanolic acid, and ursolic acid)[7,15, 32].

Therapeutic potential of *Melissa officinalis*

Over 450 million individuals worldwide suffer from various mental disorders, and 25% of the population will suffer from a mental illness during their lifetime[33]. The frequency of neurological disorders has increased in recent years, particularly in industrialised countries [34]. With recent advancements in natural product research, efforts to use complementary and alternative medicine to prevent these neurological illnesses by targeting multiple therapeutic modalities.

Antioxidant Properties of *Melissa officinalis*

A balanced redox status is important to sustained damage mediated via oxidative/ nitrosative stress. Excessive ROS and RNS can result in DNA mutation, cellular senescence, protein and lipid oxidation, and neuronal death [35]. Several *in vitro* and *in vivo* investigations have demonstrated that MO possesses potent free radical scavenging and antioxidant properties, potentially aiding in the alleviation of damage inflicted by free radicals. Its capacity to neutralise superoxide anions and nitric oxide radicals, as well as to diminish iron, bind iron, DPPH, and impede b-carotene-linoleic acid production, are among the attributes contributing to its antioxidant efficacy[18]. MO extract has a dose-dependent scavenging effect on OH°, H_2O_2, and DPPH free radicals in lipids. N-butanol extract has the highest DPPH and hydroxyl radical scavenging ability at 0.4 mg/mL and 0.5 mg/mL, with the strongest lipid peroxidation scavenging ability [36]. On the other hand, *In vitro* tests using the DPPH and ABTS also showed that the essential oil at doses of 1, 2.5, 5, and 10 mg/mL can act as an antioxidant [37]. Akbar et al., [39] reported that consuming 1.5 g of dried lemon leaves twice a day for 30 days showed significant increases in glutathione peroxidase activity, superoxide dismutase, and catalase, while DNA damage, lipid oxidation, and myeloperoxidase activity were decreased. Pretreatment of the HUVEC cell line with 100–500 g/mL of hydroalcoholic extract resulted in increased cell viability after exposure to H_2O_2 -oxidative stress[17,40]. PC12 cells when treated with ethanol extract [41] exerted an anti-oxidative property. Furthermore, hydroalcoholic extract of MO significantly reduces H_2O_2 toxicity in PC12 cells due to the inhibition of monoamine oxidase [12]. Rosmarinic acid a major component of MO depicted protective effects on skin cells in both oxidatively stress-free by decreasing intracellular ROS in human keratinocytes, thereby improving

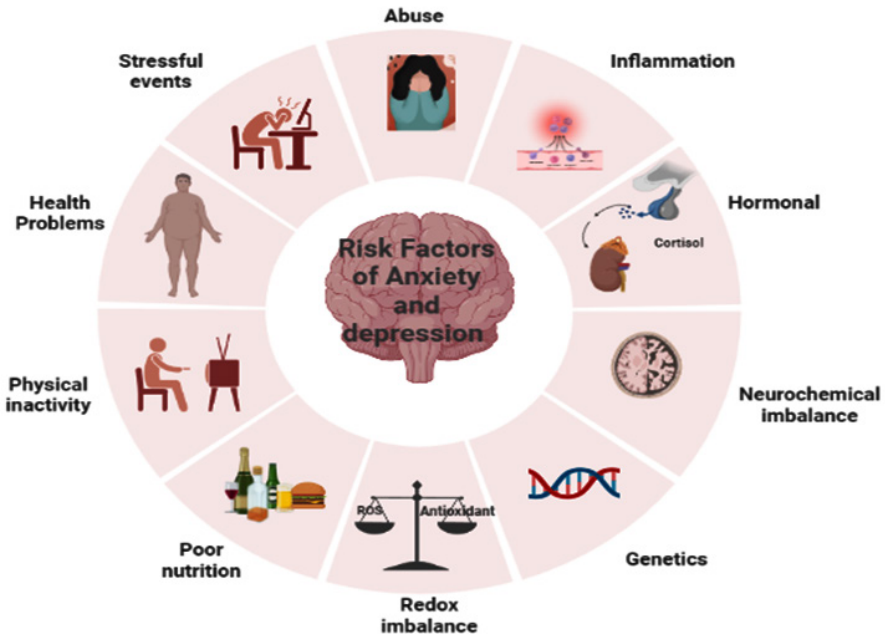

Fig. 1. Risk factor associated with anxiety and depression (Created with www.biorender.com).

cell viability [42]. MO oil diminishes antioxidant activity in the hippocampus by suppressing malondialdehyde (MDA) levels. The treatment may reduce the expression of proinflammatory cytokines such as IL-1, TNF, and HIF-1, along with the HIF-1 gene[43]. Ghazizadeh et al. [17] also illustrated that prolonged administration of the hydro-alcoholic extract at doses ranging from 75 to 150 mg/kg reduced depressive symptoms and stress-induced anxiety by mitigating oxidative stress and averting neuronal apoptosis.

Anxiolytic role of *Melissa officinalis*

MOs are often used as an anxiolytic drug, but the mechanisms underlying their therapeutic effects on plants are not yet understood (Table:2). Studies have shown that 1mg/kg of MO oil has an anxiolytic effect on the central nervous system and can help reduce stress-related anxiety. Awad et al. [44] reported that an *in vitro* investigation using rat brains revealed that an extract prepared from methanolic MO and its active component, rosmarinic acid (RA), demonstrated GABA-T blocking action when the rats were exposed to a 0-4 mg/mL MO extract. Cases et al. [45] also reported that chronic oral administration of a hydroalcoholic extract of MO to C57BL/6 mice reduced anxiety symptoms. A study conducted by Brambilla et al. [46], reported that the highest anxiolytic effect was found at 1.8 g/kg/day. Taiwo et al. [13] suggested that the Ethanol extracts have anxiolytic effects equivalent to subacute oral administration (10 days) of 300 mg/kg benzodiazepines in Wistar rats. Benzodiazepines are generally known to slow down brain activity by releasing inhibitory gamma-aminobutyric acid (GABA). Furthermore, male rats treated with MO extract showed reduced stress-like performance via GABA transaminase (GABA-T) activity. Likewise, Awad et al.[44], reported that rosmarinic acid reduces anxiety by inhibiting GABA-T activity, thereby raising GABA levels (Fig. 2).

Anti-depressive role of *M. Officinalis* extract

Literature surveys have shown the anti-depressant activity of MO (Table:2), Studies have found that supplementing with 3 g of MO for eight weeks could assist individuals with chronic stable angina to feel less depressed, anxious, and stressed out, and have a deeper sleep [47]. Taiwo et al.

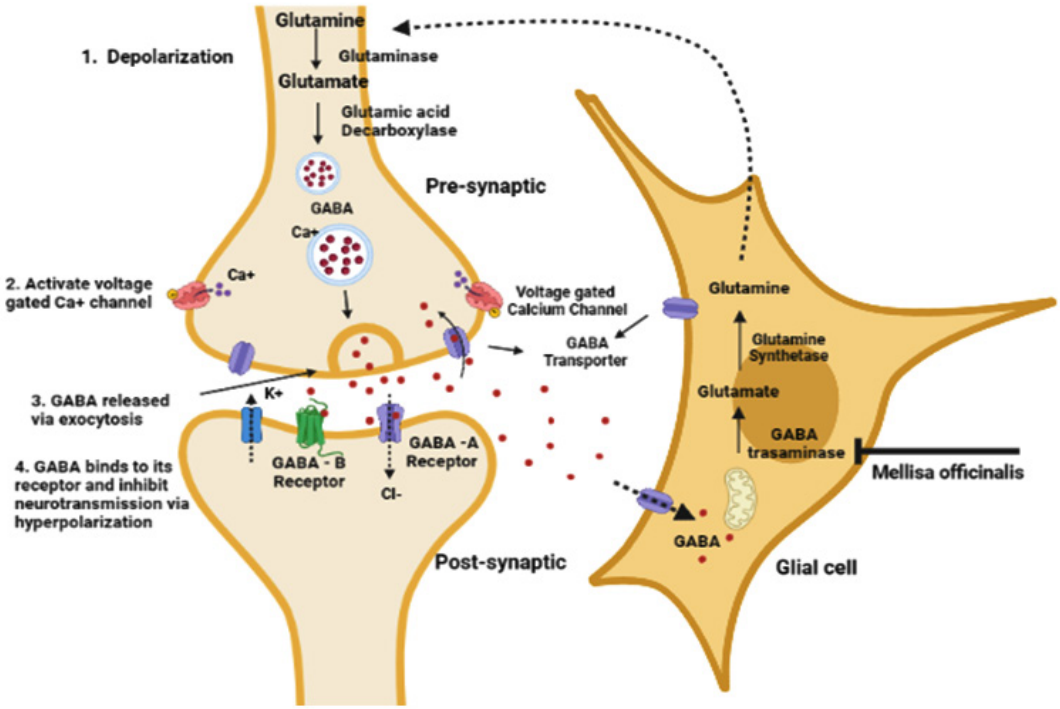

Fig. 2. GABAnergic neurotransmission and the role of *Mellisa officianalis* in inhibition (Created with www.biorender.com)

[13] reported that the ethanol extract could decrease corticosterone levels and exhibit anti-depressant benefits during the forced swimming test (FST) by increasing neurotransmission. To support our theory, an *In-vitro* study reported by López et al. [12] showed that methanol and aqueous extracts mildly inhibited Monoamine oxidase A (MAO-A) which prevents the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin. A study by Emamghoreishi and Talebianpour [48] reported anti-depressive effects like imipramine in mice and serotonergic antidepressant activity via the 'forced swimming test' in rats. Imipramine is a tricyclic antidepressant (TCA) widely used in the treatment of depression. TCA is a potent inhibitor of serotonin and norepinephrine reuptake, thereby increasing the serotonergic and noradrenergic activity necessary for neuronal transmission. However, the use of TCAs has declined in recent years, as imipramine targets multiple neurotransmitter receptors, and overdose can cause adverse side effects and toxicity. On the other hand, selective serotonin reuptake inhibitors (SSRIs) are the most prescribed antidepressants. They are selective because they mainly inhibit only serotonin reuptake into the presynaptic neurons to

Table 1. Major compounds from *Melissa officinalis*

S no.	Phyto-compounds	Composition	Reference
1	Phenolic	Rosmarinic acid, Ferulic acid, Caffeic acid, Caftaric acid, Chlorogenic acid, Gentisic acid, p-Coumaric acid, Quercetin, hesperidin, naringin, luteolin, and acids like rosmarinic acid and caffeic acid, luteolin 32 -O-D-glucuronide quinic, lithospermic acid A, malic, citric, tartaric, and succinic acid, caffeine, salicylic acid, Gallic acid,	53,54, 55, 56
2	Flavonoids	Apigenin, Hyperoxide, Isoquercetin, Kaempherol, Quercetin, Myricetin Cynaroside and Daidzein	32,52,53
3	Terpenes	Geranial, Neral, citronellal, Geraniol, Citronellol, Geranyl acetate, Camphene, Citronellal, Methyl citronellate, á-copaene, â-caryophyllene, Humulene, Caryophyllene oxide geranial, (E)-anethole and (E)-caryophyllene, linalool, limonene, thymol, ocimene, and caryophyllene, Trans-carveol, Citronellol, ä-3-carene, citronellal, Geraniol, 1-octene-3-ol, Spathulenol, Ursolic acid, Oleanolic acid, Melissioside, Betulinic acid, Ursolic acid, 23-sulfate ester of 2á,3â,19 á,23-tetrahydroxyurs-12-en-28-oic acid 28-O-â- D-glucopyranoside, 23-Sulfate ester of niga-ichigoside F1 3,23-Disulfate ester of 2á,3â,19á,23-tetrahydroxyurs-12-en-28-oicacid 3,23-Disulfate ester of2á,3â,23,29-tetrahydroxyolean-12-en-28-oicacid 3â,16â,23-Trihydroxy-13,28-epoxyurs-11-ene-3-O-â-D-glucopyranoside	19, 44, 57, 58, 59,60, 61
4	Other Essential oils	(E)-caryophyllene, caryophyllene oxide, thymol (E)-citral, methyl geranat, trans-caryophyllene, 3-octanone 3a,4,5,7a-tetrahydro4-hydr-1(3H)-isobenzofuranone a, cis2H-3a-methyl-octahydro Inden-2-one, citronellal, methyl palmitate, neral, trans-paramentha-1(7),8-dien-2-ol, trifluoroacetyl lavandulol, 1-Octen-3-ol, Valencene, Trans-Rose oxide, Trans –Limonene oxide, Piperitone, n-Nonanal, n-Heneicosane, Nerol, Neral, n-Eicosane, Myrcene, Menthol, Isomenthol, Germacrene D, Dihydrocitronellol acetate, Citronellal Cis-Chresontynol, Cis -Rose oxide, Caryophyllene oxide, Camphor, b-Cubebene, b-Caryophyllene, a-Humulene, a-Cubebene, a Copaene, 6-Methyl-5-hepten-2-one, 1-Hexadecene, 14-Hydroxy-9-epi-(E) Caryophyllene, (Z)-b-Ocimene, (E)-Nerolidol, (E)-b-Ocimene, (E)-b-Ionone, Myrcene, Methyl geranate, Methyl eugenol, Methyl citronellate, Menthol, Isomenthol, Isogeranial, Humulene epoxide II, Germacrene D, Dihydrocitronellol acetate, Citronellyl acetate, Myrcene, 6-Methyl-5-hepten-2-one, Alloaromadendrene, Neral, (E)-Methyl Geranate,	57, 62, 63,64

Table 2. Anxiolytic and anti-depressive activities of *Melissa officinalis* extracts and its phytocompounds

S no.	Activity	Solvent/ compound	Dosage and study model	Mode of action	References
1	Anti-anxiety	Ethanolic extract	0, 30, 100, or 300 mg/kg oral(10-day course using Male and female Wistar rats)	Anti-anxiety effects are comparable with benzodiazepines as the dosage increases irrespective of male and female rats	13
		Melissa officinalis L. extract (Cyracos®, Naturex)	240 mg/kg and 360 mg/kg Chronic oral administration in C57BL/6mice	Anti-anxiety effects are linked to the inhibitory activity of Cyracos and its components on GABA-T, increasing the availability of GABA in the brain.	66
		MO extract (SA, Lugano, Switzerland)	Double-blind, placebo-controlled, randomized (300 and 600 mg) oral administration in human	MO has the potential to alleviate the effects of anxiety.	20
		Hydroalcoholic extract	50, 75 and 150 mg/kg b.w. using Albino BALB/c male mice	Block the mechanisms that lead to oxidative stress and apoptosis in the prefrontal and hippocampus, reversed anxiety- and depressive-like behaviors.	17
			(Cyracos) 300 mg twice a day for 15 days	Inhibit gamma-aminobutyric acid	45
2	Anti-depressant activity	Capsules containing MO (Powder)	3 g MO supplement or placebo daily for 8 weeks. A double-blind plaacebo-controlled clinical trial with chronic stable angina (CSA)	Patients with CSA who used MO reported better sleep efficiency, length, and quality.	47
		Dried powder of lemon balm, placebo	Randomized, Triple-blind, placebo-controlled, clinical trial, Capsule 500 mg (3 times a day) 10 days. C-section patients who were hospitalised	Compared to the placebo group, the therapy group had a decreased incidence of postpartum depression.	66
3	Anti-stressor	Aqueous extract	200 mg/kg oraladministration in male mice	Decrease plasma . corticosterone levels	67

improve serotonergic transmission. MO aqueous extract and rosmarinic acid treatment increased swimming time and decreased serotonin turnover in rats, thus suggesting that MO could treat depression [49]. Essential oils like geranial, neral, citronellal, geraniol, eugenol, and tannins were shown to have potent antidepressant effects [50-51]. Safari et al. also suggested that the administration of 700 mg/day of hydroalcoholic extract may lead to improvements in depression and sleep quality among patients with type 2 diabetes mellitus and symptoms of depression[52].

CONCLUSION

We have reviewed the pharmacological properties of *Melissa officinalis*, on anxiolytic, antidepressant, and antioxidant activities. MO extracts have shown antioxidant activity by effectively scavenging free radicals. Rosmarinic acid, a major constituent can promote the longevity of the cells by staving off oxidative stress and reducing cellular apoptosis, inhibitory effects on Gamma-Aminobutyric Acid Transaminase (GABA-T) to reduce neuronal excitability. It can also decrease serotonin reuptake in presynaptic neurons for serotonergic transmission and inhibit monoamine oxidase A (MAO-A) to prevent oxidative deamination. Further studies on the receptor subtypes are still needed to understand the mechanisms underlying the pathogenesis of this disorder.

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Conflict of Interest

The authors confirm that they have no conflict of interest to disclose.

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Authors' Contribution

Lipoksenla: Principal author, Viswedenu Kera: Data collection Sunit Nath: Data collection, Avolu Kotso: Data collection, Vekutolu Resuh: Data collection, Abhijit Dutta: Data collection, Wankupar Wankhar: corresponding author

Data Availability Statement

Not applicable.

Ethics Approval Statement

Not applicable.

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