Melissa officinalis L. in the Management of Anxiety: Phytochemistry, Mechanisms of Action and Development of Herbal Chocolate as a Novel Functional Delivery System

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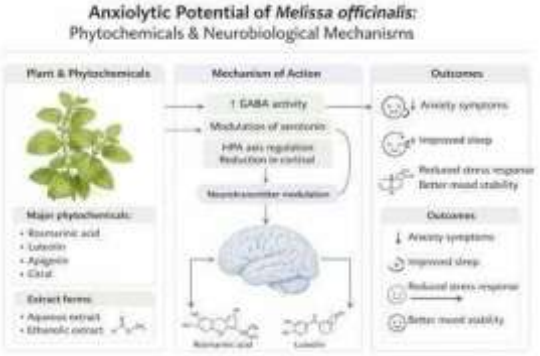
Abstract:
One of the most important neuropsychiatric burdens on the globe with immense functionality and lower quality of life is anxiety disorders. Although benzodiazepine and the antidepressants treatment is the primary gateway of treatment currently, its usage is still associated with negative adverse effects, that include sedation, cognitive dysfunction, tolerance, dependency and withdrawal symptoms due to long-term use of it. These adverse effects of treatment have led to a growing scientific interest in safer and more tolerable analogs of plants.
as alternative or complementary treatments that are less risky and which are more acceptable to the patient.
Lemon balm Melissa officinalis L. is a perennial aromatic herb, which is a member of Lamiaceae family. It is a proven cure of anxiety, nervous tension, sleeplessness, and stress-related disorders. The scientific studies have shown that the plant has large concentration of bioactive phytoconstituents that include rosmarinic acid, derivatives of caffeic acid, flavonoids including luteolin, quercetin, phenolic compounds and volatile essentials oil like citral and citronellal. These components are said to contain anxiolytic, sedative, antioxidant, and neuro protectant effects of non- similar gamma-aminobutyric acid (GABA)ergic action, reduction of oxidative stress as well as control of neurotransmitter pathways as a component of mood stabilization.
Simultaneously, the introduction of the functional foods concept has been a novel approach to administration of the therapeutic agents in a more palatable and desirable form. Due to high palatability, lipid-rich composition, and natural ability of chocolate to increase the mood, chocolate can be a great carrying system to add herbal extracts. Rossum fractionation would increase compliance with extract consumption and taste and taste of the extracts and may be synergistic in the treatment of anxiety.
The paper in the review expounds the botanical properties, phytochemical properties, pharmacology, extraction method, and possible application of Melissa officinalis in herbal chocolates formulations as a novel functional ingredient and anxiogenic agent. The safety and effectiveness of it in the long term should be established by more clinical and formulation studies.



Graphical Abstract. Overview of the anxiolytic potential of Melissa officinalis highlighting phytochemicals and proposed neurobiological mechanisms.

Keywords:- Anxiety, Melissa officinalis, Lemon balm, Herbal chocolate, Anxiolytic activity, Functional food, Phytochemistry.

Introduction : The process of anxiety is an evolution process that is adaptive, but the maintenance of anxiety is more than the physiological threshold, which leads to pathological manifestations. But a step further when the anxiety goes chronic and excessive and inappropriate to the realities on the ground, it then advances to the anxiety disorders. Disorders are not only one of the most common psychiatric disorders in the world, but one of the most serious public health problems on the sense that it is extremely prevalent and long-term consequences in terms of its effect on the quality of life. Clinical manifestations of the symptoms of anxiety disorders are the worrying that constantly occurs, the fear, the agitation, sleeplessness, the irritability, and the inability to concentrate. Uncontrolled continuous anxiety could have negative implications in terms of educational performance, job output, relationships with others, and mental well-being.

Dependency and cognitive side effects, predominantly benzodiazepines, SSRIs, and SNRIs selective serotonin reuptake, serotonin-norepinephrine reuptake and other anxiolytic drugs have a probability of taking place during the long-term treatment. Although these drugs have been seen to be effective in treating the symptoms, with continued use, they are normally linked with restrictions such as sedation, psychomotor retardation, cognitive impairment, tolerance, dependence and withdrawal effects. The above has brought about a growing interest in complementary and alternative therapeutic interventions that are less harmful and less objectionable.

The use of herbal medicines has been seen as attractive alternatives because it was naturally available and that had been used in the past in the traditional system of medicine, and its safety profile was quite good. One of them, Melissa officinalis L., otherwise known as lemon balm, has had a lot of publicity in terms of its calming and stress relieving effects against the nervous system. It is a traditional herb which is used in the treatment of anxiety, lack of sleep, nervous tension, mood disturbances, and many others. It is of the Lamiaceae family. As per the existing pharmacological research, its bioactive formulations can be applied in its anxioly, sedative, antioxidant, and neuroprotective effect. Due to this accumulated body of science, Melissa officinalis is turning out to be a great target of plantbased therapy in the treatment of anxiety.

Botanical Description and Taxonomical Profile of Melissa officinalis L. :

Lemon balm Melissa officinalis L. is a perennial aromatic medicinal herb that has been chosen as a herb that is a member of the Lamiaceae family. Melissa genus is very species-limited and the most studied and used as a source of therapeutic utilization is Melissa officinalis. Its long history of traditional use as a pharmacopeia in Europe can be seen in the meaning of its species name that it is an officinalis.

Figure : Morphological and botanical features of Melissa officinalis L.

Taxonomical Classifications

Rank	Classification
Kingdom	Plantae
Division	Magnoliophyto
Class	Magnoliopsida
Order	Lamiales
Family	Lamiaceae
Genus	Melissa
Species	Melissa officinalis L.

The glandular oil-rich trichomes of the plant have a low inter-relation with the other medicinal genera of Lamiaceae including Mentha, Ocimum, and Salvia.

Morphological Characteristics -

Melissa officinalis is a perennial, bushy, and herbaceous plant which may reach 30150 cm in a favorable environment. The morphological characteristics of the plant are:

Stem -

It is straight stemmed, quadrangular shaped (as well as Lamiaceae), branched, and fine glandular highs. The nature of the oil released into these glandular trichomes are volatile essential oils, the origin of the lemon odor of the plant.

Leaves -

The leaves are opposite and heart-shaped and elliptric with a length of between 5-9 cm. To some degree, they have serrated sides and wrinkled surface. The glands of oil are the surface of the leaf, and they produce essential oils which are rich in citral and citronellal. The most popular medicinal component is the leaves, and it is used in the preparation of the therapeutic preparations.

Flowers -

It is a small bilabiate (two-lipped) flower of pale yellow white colour. The axillary clusters carry the blooming, and the flowers are usually not only seen in late spring and early summer. The most common pollinator is the bee, and this is denoted in the name of the plant which has the Greek word of honeybee Melissa.

Roots -

This branched fibrous root system is thus flexible to the temperate weather conditions.

Geographical Distribution and Cultivation:

Melissa officinalis is native to Southern Europe and Western Asia and Mediterranean. It is currently extensively grown in temperate Europe, North America, Asia and the limited parts of Middle East because of the health and business importance.

The plant prefers:

- Well-drained loamy soil
- Moderate sunlight exposure
- Temperate climatic conditions

The soils have optimal growth in slightly alkaline to neutral ph. I The environment sensitive essential oils and phenolic compounds include altitude, temperature, the nature of the soils and the season during which they are harvested and therefore they can have varied amounts of concentration as might apply to the environmental factors.

Microscopic Characteristics :

Microscopically, the leaf exhibits: ▪ Diacytic stomata

▪ Multicellular covering trichomes

▪ Glandular trichomes containing essential oils ▪ Prominent vascular bundles

It is also noteworthy that the glandular trichomes are also the site with the greatest concentration of the trichomeres as the main site of the monoterpenes production and storage.

Chemotypes and Variability :

Melissa officinalis can change its chemical composition depending on its geographical location, the method in which it is cultivated. The most important compound is citral which changes in the various chemotypes; the change is pegged on the different concentrations of citral (neral and geranial isomers).

Scientific Significance in Pharmacognosy :

This type of phytochemical variation affects the pharmacological activity and the pharmacological standardization:

▪ Organoleptic evaluation

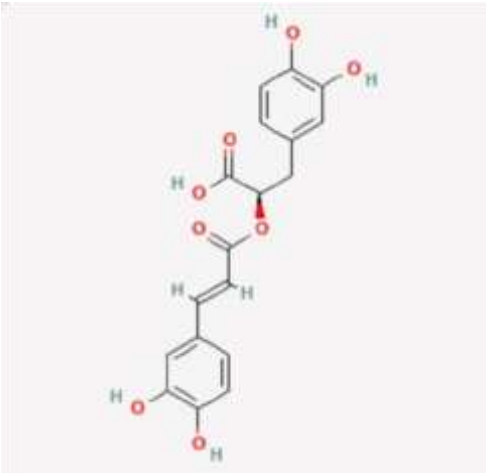
▪ Microscopic examination

▪ Determination of total phenolic content ▪ Essential oil profiling

Proper authentication ensures consistency in therapeutic outcomes and supports regulatory compliance for herbal formulations.

Phytochemistry of Melissa officinalis L. :

Melissa officinalis has been credited with its pharmaceutical properties, which are largely because of its wide spectrum and chemically endowed profile of phytoconstituent. It is abundant in bioactive secondary metabolites that are tannins, volatile essential oils, phenolic acids, flavonoids, terpenoids, and volatile essential oils. The correlation of these compounds leads to anxiolytic, antioxidant, sedative, and neuroprotective activity.



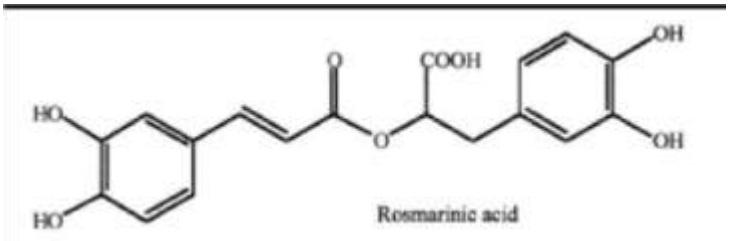


Figure : Principal bioactive compounds identified in Melissa officinalis.

Phenolic Compounds:

Phenolic acids are the most important chemical compounds in Melissa officinalis. Rosmarinic acid, the most common bioactive phenolic marker of them has been reported to be the major contributor of the neuroprotective and anxiolytic effects of the plant. It has a very good antioxidant and neuro- protective effect. The other phenolic acid components that are found in low concentration include caffeic acid and chlorogenic acid. Rsmaric acid is reported to be able to:

Group 9395 Grouped objectInhibit oxidative stress:

- Inhibit oxidative stress
- Protect neuronal cells
- Contribute to calming effects

The concentration of phenolic compounds depends on extraction method, plant age, and environmental conditions.

Flavonoids :

Flavonoids such as luteolin, apigenin, and quercetin are present in the leaves. These compounds exhibit:

- Anti-inflammatory activity
- Neuroprotective effects
- Modulation of neurotransmitter systems

Flavonoids also enhance antioxidant defense mechanisms and support overall brain function.

Essential Oils :

The essential oil fraction contains volatile monoterpenes including:

- Citral (neral and geranial)
- Citronellal
- Linalool
- Geraniol

These volatile constituents are mainly responsible for the plant's characteristic lemon aroma. Essential oils contribute to mild sedative and relaxant effects through central nervous system interaction.

Serotonergic and Cholinergic Modulation:

Weaker alterations of serotonin systems, to which mood control is attributed, are called forth in preclinical research. Moreover, mild amounts of acetylcholinesterase inhibition have taken place that are likely to bring in better performances of cognitive abilities. In so doing its general anxiolytic effect is multifactorial and synergistic.

Clinical Evidence on Anxiety:

Pilot-scale and pilot randomized clinical trials are statistically significant and have valid measures of the anxiety assessment. Nonetheless, the authors of the study by Hadges et al. (2016) discovered that inter-study comparability has certain limitations because of the varying degrees of extract standardization and alternative dosing regimens.

Experimental Studies :

Animal models have demonstrated:

- Reduced anxiety-like behavior
- Increased time spent in open-arm maze tests
- Improved stress tolerance

These findings support its calming and sedative properties.

Human Clinical Studies :

Small-scale clinical trials have reported:

- Reduction in self-reported anxiety scores
- Improvement in sleep quality
- Enhanced calmness and relaxation

The outcomes of certain trials conducted with the use of placebo control proved that the participants exposed to the standardized Melissa officinalis extract experienced significant reduction of the symptoms of mild to moderate levels of anxiety in comparison with the placebo. Interestingly, there were minimal negative effects, and no major safety concerns were being reported when short-term studies were being conducted.

Limitations of Current Evidence :

Despite promising results, limitations include:

- Small sample sizes
- Short duration of studies
- Lack of large-scale randomized controlled trials

This way, the current data has demonstrated the anxiolytic promise, and more structured clinical trials are to be carried out to understand the long-term effectiveness and standardize the dosage regimen.

Discussion:

As can be seen in the current review, Melissa officinalis L. has some promise as a natural remedy in treating anxiety. The available phytochemical and pharmacological evidence indicate that the plant is multi-dimensional in mode of action, which could be described as the GABAergic modulation, antioxidant defense and antagonistic serotonergic behavior. The Melissa officinalis seems to have a more balanced and milder neuroslowing effect compared to the conventional anxiogenic compounds, which typically have a single action route, and thus, it is addictive or sedative. The center of anxiolytic activity is the presence of rosmarinic acid and its high percentage of bioactive components.

Its antioxidant action will be handy in averting the oxidative injuries of the neuronal cells that are connected with chronic stress and anxiety disorders. Also, it is a relaxing substance because volatile substances like citral and citronellal are also engaging in communication with the central nervous system.

The idea of introducing Melissa officinalis extract into herbal chocolate is a novel idea in the functional foods sector that is concerned with controlling anxiety. Chocolate is a lipid-rich matrix with the potential to stabilize and bioavailability of some of the phytoconstituents. Moreover, its good taste and the ability to enhance the mood will help it to reach a higher level of compliance among patients who are unwilling to use more traditional medications.

The evidence is however, poor even though the results of the experiment and the preliminary clinical results were favorable since the sample sizes in which the experiments were done were small and the duration the study took was short. Standardization of extract composition and dosage is a very crucial requirement in clinical translation.

Altogether, Melissa officinalis has a high potential as a complementary therapeutic agent, but a strict scientific validation of this fact is needed.

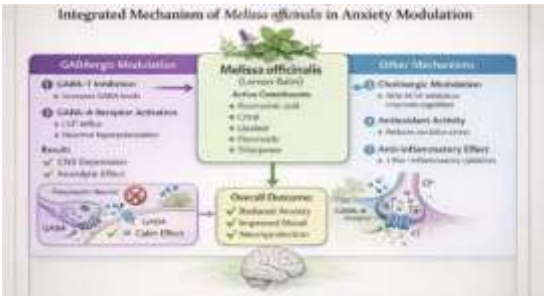


Figure : Integrated model summarizing the proposed neurobiological mechanisms of Melissa officinalis in anxiety modulation.

Limitations :

Although the scientific sources on the material under discussion witness the anxiolytic effects of Melissa officinalis, several limitations should be taken into consideration:

The clinical research is mainly done on small samples.

Most of the trials are short hence they cannot give the long-term safety check.

The differences in the extraction procedures cause the possible imbalance in the phytochemical composition.

Lack of standardized dosage.

Inappropriate pharmacokinetic and bioavailability data. Poor large-scale randomized controlled trials.

These shortcomings do restrict final findings regarding its effectiveness as a first line of intervention in treating anxiety disorders.

Future Directions :

Further research in this direction ought to be oriented to rigorously planned, double-blind randomized controlled experimental research based on standardized phytochemical quantification and long-term safety research.

▪ Establishing standardized extract formulations based on quantified rosmarinic acid content. ▪ Evaluating long-term safety and tolerability.

▪ Investigating pharmacokinetic properties and bioavailability. ▪ Studying herb–drug interactions.

▪ Exploring optimized herbal chocolate formulations for stability, dose uniformity, and controlled release.

In addition, the sophisticated analytical techniques that could be used to ensure quality control and standardization are the high-performance liquid chromatography (HPLC) and the mass spectrometry. It could be helpful to combine ancient medicinal knowledge with the current pharmaceutical technology in the development of evidence based herbal therapy.

Conclusion :

Melissa officinalis L. is a medicinal plant with enormous prospects in the treatment of stress and anxiety disorder. It is anxiolytic, antioxidant, and neuroprotective due to its pharmacological multiplicity in terms of a high concentration of phytochemicals and flavonoids, more specifically, rosmarinic acid, flavonoids, and essential oils. The GABAergic system modulation, as well as the loss of oxidative stress, is the mechanism of its action that should be considered in the framework of the mechanistic evidence.

Even though the clinical evidence is still positive, more detailed clinical trials are required to prove effectiveness, most effective dosage, and the safety of long-term use. The Melissa officinalis extract herbal chocolate is a new and patient friendly functional methodology, which could increase the level of

compliance and treatment compliance.

Melissa officinalis may also be useful in addition to anxiety therapy if it is unquestionably standardized and scientifically proved.

Herbal Chocolate Formulation Concept

Melissa extractt
Standardization (Rosmarinic acid %)t
Incorporation into chocolate baset
Stability testingt
Anxiolytic functional product Caption:

Figure X. Proposed development pathway of Melissa officinalis incorporated herbal chocolate formulation.

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