# Lemon Balm

*Melissa officinalis*

## AN OVERVIEW OF ITS BIOLOGICAL ACTIVITIES AND MECHANISM OF ACTIONS

**Scientific report**
authored by

groupe berkem

***Melissa officinalis* L.** (Greek word "Melissa"— honeybee) or **lemon balm** is a widespread plant that is sometime considered as a weed by gardener as the plant spread so easily in different type of climate and soil. Lemon balm possesses diverse **biological** and **health properties** depicted in **traditional medicine** and confirmed in **preclinical** and **clinical studies**. Amongst them, its effects on **sleep** and **anxiety disorders** [1].

Both of these disorders are considered nowadays important burdens for the population as in 2019, the World Health Organization reported that the total estimated number of people with anxiety disorders in the world was 301 million [2]. The figures regarding sleep disorders are also concerning. The data from the National Health Interview Survey in 2020, reported that 14.5% of American adults had trouble falling asleep and 17.8% of adults had trouble staying asleep most days or every day in the past 30 days [3]. Even **several medications are known** for years to help people, read out of those problems, **several sides effects** are documented [4]. Find complementary and safe approaches to relieve anxiety and its often-associated symptoms, like sleep disorders, need to be explored.

# Physiology and management of anxiety

## > Definition of anxiety and classifications

**Anxiety** is considered normal when it plays an **adaptive role**, allowing the subject to prepare for the occurrence of and response to threatening or unusual stimuli. Most anxieties dissipate fairly quickly without leaving a psychological mark.

On the contrary, **chronic anxiety** can be suggested as soon as the symptoms are too frequent, intense or inappropriate and when an impact on the subject's ordinary activities (family, professional environment, environment, leisure) is observed. They are generally characterized by excessive anxiety, feelings of fear, worries and behaviors that are context-dependent [5]. Those anxiety disorders have been classified in the **Diagnostic and Statistical Manual of Mental Disorders** (DSM) and exhibit diverse phenotypes in humans [5,6]. Eight phenotypical categories are described: general anxiety disorders (GAD), panic disorder, agoraphobia, post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), acute stress disorder (ASD), separation anxiety disorder, and obsessive–compulsive disorder (OCD).

Whatever their intensity, the clinical manifestations of anxiety are usually defined as **three different categories**:

- **psychological**: worry, irritability, attention and concentration difficulties;
- **somatic**: tachycardia, palpitations, digestive disorders, insomnia, fatigue, and sleep disorders;
- **behavioral**: hyperactivity, compulsions, and rituals.

While genetic predispositions and individual personality traits can increase one's vulnerability to anxiety disorders, a variety of life events may also trigger their development. For instance, experiencing a serious illness, the loss of a loved one, navigating a new or unstable professional environment, enduring a traumatic event, or being involved in an accident can all contribute to the onset of anxiety disorders.

As anxiety disorders have many faces, the **physiological mechanisms** involved in the physiopathology of anxiety disorders are also **complex** and often **interrelated**. They arise from the interaction of various **neurotransmitter pathways** within the **central nervous system**. It is primarily mediated by the limbic system, particularly the amygdala and prefrontal cortex, which regulate emotional responses and cognitive appraisal of stressors. The **autonomic nervous system** also plays a crucial role, with heightened **sympathetic activity** contributing to the physical symptoms of anxiety, such as increased heart rate, sweating, and hypervigilance.

## > Brain structures and physiological pathways altered in anxiety

### The importance of the limbic system

The limbic system is a complex network of interconnected brain structures involved in emotion, memory, and behavior regulation (Figure 1). It includes key components such as the **hippocampus**, which plays a crucial role in memory formation and spatial navigation, and the **amygdala**, which is essential for processing emotions, particularly fear and threat-related responses. The **hypothalamus** regulates autonomic and endocrine functions, maintaining homeostasis and linking the nervous system to the endocrine system via the pituitary gland.

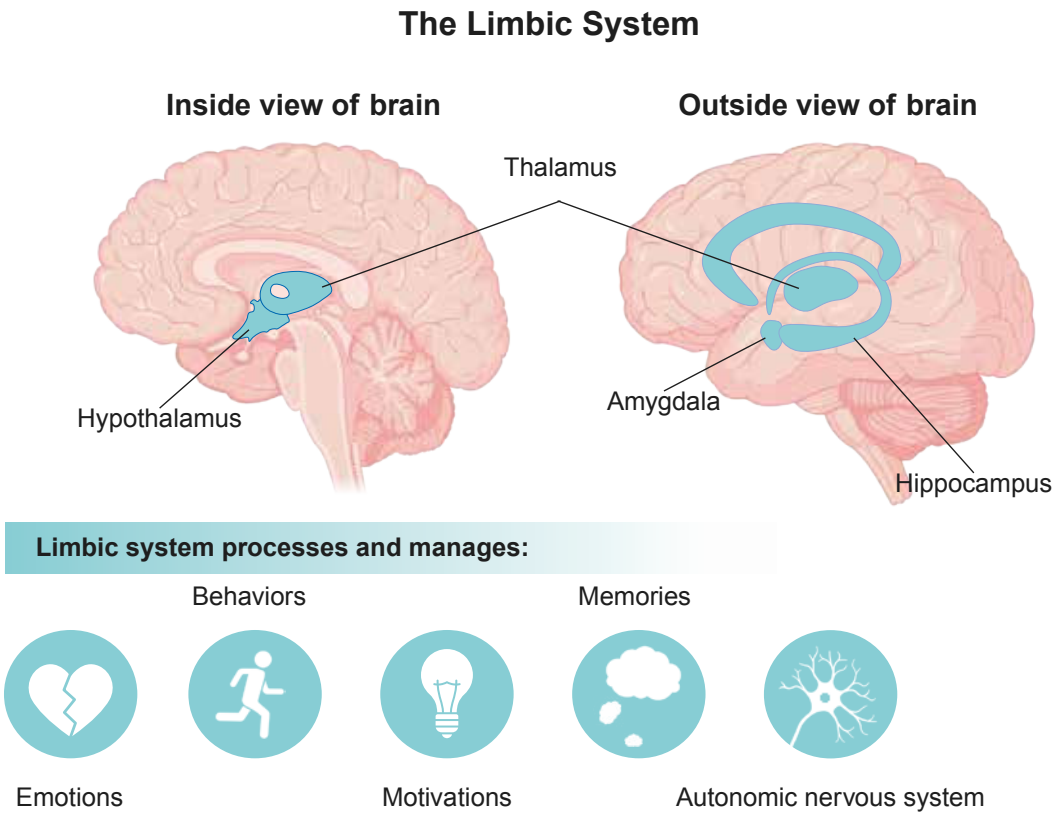


Figure 1: The limbic system (https://my.clevelandclinic.org/health/body/limbic-system).

**Dysfunction in the limbic system** and the associated neuronal connectivity has been associated with various **neurological** and **psychiatric disorders**, including anxiety, depression, and neurodegenerative diseases.

## Gamma-aminobutyric acid (GABA) neurotransmitter

Gamma-aminobutyric acid (GABA) is the **brain's primary inhibitory neurotransmitter**, playing a crucial role in **reducing excessive neuronal excitability**, likely through interactions with other neurotransmitter systems [7]. GABA functions through various receptor subtypes, with the postsynaptic **$GABA_A$ receptor** being the most significant. When activated, it facilitates chloride ion influx to conduct the signal. Reduced GABAergic activity has been observed in both anxiety disorders and severe depression [7]. Functional brain imaging studies in individuals with depression have revealed lower GABA levels in cortical regions, while animal research has shown that decreased expression of receptors ratio led to anxiety-like behaviors. Consequently, the **GABAergic system** has gained considerable attention as a **potential therapeutic target** for **anxiety** treatment. For instance, benzodiazepines enhance GABAergic transmission by increasing the receptor's affinity for GABA, producing strong sedative and **anxiolytic effects**. Another strategy to modulate GABAergic transmission and alleviate anxiety symptoms involves **elevating GABA levels** in the brain. This can be achieved by **inhibiting GABA transaminase** (GABA-T), the enzyme responsible for GABA catabolism [8].

## Mono-aminergic neurotransmitters

An increasing body of research highlights the involvement of dysfunction in monoaminergic neurotransmitters — specifically the **serotonergic**, **noradrenergic**, and **dopaminergic systems** — in the neurobiological mechanisms underlying major depressive disorder (MDD) and anxiety disorders. The physiological disturbances leading to abnormal signaling of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) may stem from either a decreased presynaptic release of these neurotransmitters or disrupted signal transduction (Figure 2). These alterations can, in turn, affect receptor regulation, receptor function, or intracellular signaling processes [8]. **Monoamine oxidase A** (MAO-A) plays a key role in the central nervous system by **regulating the levels** of all three major **monoamine neurotransmitters** in the brain [9]. Notably, **inhibiting MAO-A activity** has been associated with the **reduction of depressive** and **anxiety symptoms** [10].

## The hypothalamic-pituitary-adrenal (HPA) axis

The hypothalamic-pituitary-adrenal (HPA) axis is a central neuroendocrine system that plays a **critical role** in the **stress response** and the physiology of anxiety. Activation of the HPA axis **triggers the adrenal glands** to release **cortisol**, the primary stress hormone [12,13]. Elevated cortisol levels enhance alertness and help the body respond to acute stressors. However chronic **dysregulation of the HPA axis**, particularly prolonged hypercortisolemia, has been associated with increased **anxiety symptoms** and **stress vulnerability** (Figure 2). High cortisol levels can exacerbate anxiety by enhancing amygdala activity and impairing the regulation of emotional responses by the prefrontal cortex. Additionally, **excessive cortisol** has been shown to reduce serotonin synthesis and receptor sensitivity, further contributing to **anxiety** and **mood dysregulation**. Therapeutic interventions that target HPA axis regulation, such as mindfulness-based stress reduction and pharmacological agents that modulate cortisol levels, may help in managing anxiety disorders effectively [12,13].

## Acetylcholine neurotransmitter

Acetylcholine is an **essential neurotransmitter** that plays a pivotal role in the peripheral nervous system by **facilitating muscle contractions** and **regulating autonomic functions**. Acetylcholine plays also an essential role in the central nervous system [14]. Indeed, cholinergic neurons have been identified in various brain regions involved in mood regulation including the hippocampus and amygdala. Acetylcholine plays its role through its interactions with **nicotinic** and **muscarinic receptors**. In anxiety, dysfunction of these receptors can lead to **altered cholinergic signaling**, affecting **arousal** and **stress responses**. The balance between muscarinic receptor activation and inhibition is crucial for maintaining emotional stability, as excessive cholinergic activity can lead to increased anxiety and stress-related behaviors [15].

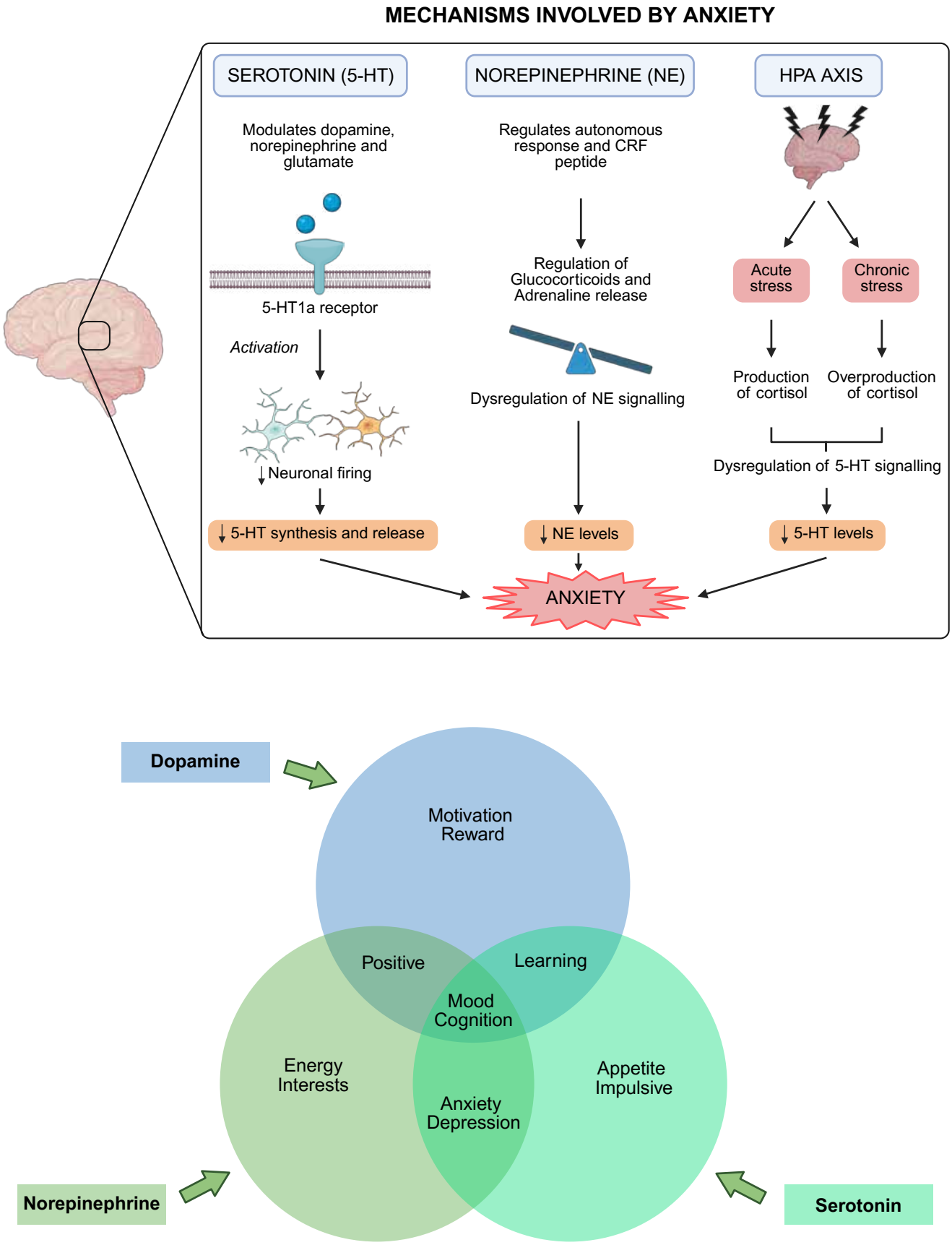


Figure 2: Representation of various mechanisms involved in anxiety. 5-HT1a receptor activation plays a role in anxiety by decreasing firing rate of 5-HT neurons, suppressing synthesis and release of 5-HT leading to anxiety. NE is important in regulation of autonomic responses and decreased level of NE results in anxiety. HPA axis activates in response to stress resulting in a production of cortisol which affects serotonergic system leading to anxiety (Khatri et al., 2020) [11].

## Oxidative stress

The brain is highly susceptible to **oxidative stress** due to its high oxygen consumption, limited antioxidant defenses, and lipid-rich composition [16,17]. When oxygen-derived metabolites exceed the brain's protective mechanisms, **oxidative damage** can affect brain function and more particularly **reduced membrane fluidity** and impaired receptor, enzyme, and ion channel function [16,17]. This disruption can **alter neurotransmission**, neuronal activity, and overall brain function, potentially contributing to inflammation, neurodegeneration, and neuronal death that have been associated in the **physiopathology of anxiety** [16,17].

Lastly, **neuroinflammation**, that will be not developed here, is also associated with anxiety. Recent studies suggest that anxiety symptoms represent brain alterations caused by neuro-inflammation [18]. Indeed, various **pro-inflammatory cytokines**, including interleukin 1β (IL-1β), interleukin 6 (IL-6), iNOS (inducible nitric oxide synthase) and tumor necrosis factor alpha (TNFα), are enhanced in different types of anxiety disorders [19].

Several pharmacological agents, such as **benzodiazepines**, are commonly prescribed to **manage anxiety disorders** and associated symptoms. Although these drugs are highly effective, their long-term use is often associated with adverse effects, including cognitive impairment, sedation, respiratory depression, and withdrawal symptoms, as well as the development of tolerance and dependence [10–13]. To mitigate these risks, **phytotherapy** has emerged as a **complementary approach**, particularly for individuals with moderate symptoms. Among botanical extracts, ***Melissa officinalis*** (lemon balm) has been **traditionally used** to alleviate **anxiety**, offering the potential for fewer side effects while maintaining therapeutic efficacy. This natural alternative is **increasingly recognized** as a valuable adjunct to conventional medication in managing mood disorders.

# > Lemon balm

## Description

Lemon balm belongs to the mint family Lamiaceae, is widespread in the natural flora of the Mediterranean region, southern Europe, North Africa and as far east as the Caucasus and northern Iran. Lemon balm is a long-stumped herbaceous aromatic perennial plant, 30 to 80 cm high. Opposite, oval leaves are dark green above, paler below. White flowers appear from June to September at the base of the upper leaves. The fruit, surrounded by a husk, contains shiny dark-brown seeds.
The plant is abundant in essential oils such as citral, citronellal, and geraniol, which are responsible for its distinct lemon aroma. In addition, lemon balm encompasses a diverse array of phytochemicals, including **phenolic compounds** like rosmarinic acid, caffeic acid, and ferulic acid [20, 21]. **Flavonoids**, namely luteolin, apigenin, and quercetin, are also present and are known to contribute to its **calming** and **neuroprotective properties**. Moreover, the plant contains tannins, terpenes, and triterpenes, along with minor quantities of coumarins, all of which enhance its antimicrobial and antiviral characteristics [20, 21]. Despite the wide range of phytochemicals found in lemon balm, **rosmarinic acid** has emerged as the **main biomarker** for plant standardization and quality control, owing to its relatively high concentration compared to other constituents [22, 23].

## Biological properties of lemon balm

As reported in several monographies, lemon balm has been **used traditionally** to aid digestion, soothe abdominal pain of digestive origin and as a carminative for **gastrointestinal disorders**. It has also been described to help **maintain a positive mood** and to contribute to a good and calm rest [22, 24]. **Lemon balm** is also traditionally used to help fall asleep and **reduce nervousness**, especially in cases of sleep disorders [22, 24].
The **scientific literature** confirmed those traditional uses and effects. In preclinical studies, oral administration of different types of **lemon balm extracts** (ethanolic, hydroethanolic or water extracts) induced **anxiety-like behavior improvement** [25, 26]. In an animal model of depression- and anxiety-like behavior by restraint stress, the administration of a **standardized rosmarinic acid** (RA) hydro-alcoholic extract of lemon balm (50, 75 and 150 mg kg–1 day–1) was evaluated for 14 days. The administration of the lemon balm extract, at doses of 75 and 150 mg $kg^{-1}$ (containing 3.825 and 7.650 mg RA), improve significantly anxiety-like behavior evaluated in the different test used (open field task, elevated plus maze, tail suspension and forced swimming tests) [26].

Lemon balm has also been **tested in humans** for **relieving anxiety** and **insomnia**.

The **acute effect** of different single doses (300 – 1600 mg/dose) of **lemon balm on anxiety** has been tested in normal and stress conditions in healthy subjects. If the sole dose of 300 mg has **positive effect 1h after the ingestion** of the lemon balm extract without stress induction, 600 mg seems necessary to have the same effect in people that have been exposed to a standardized battery of stressors (DISS: Defined Intensity stressor Stimulation) [27]. The chronic effect of lemon balm was also tested in different clinical studies. In a prospective, open-label study, twenty healthy adults with mild to moderate anxiety and sleep disorders were recruited to test the effect of lemon balm during 15 consecutive days. Each participant took 600 mg of lemon balm extract daily (divided into two equal doses), which contains mainly rosmarinic acid. The results showed that 70% of the participants achieved complete **anxiety remission**, 85% for **insomnia**, and 70% for **both conditions** [28].

Lemon balm — alone or in combination — has been tested in specific population like woman with premenstrual syndrome or menopausal symptoms but also in post-surgery. Lemon balm alone (2 x 500 mg/day) taken during two consecutive menstrual cycles, demonstrated positive effect on **premenstrual syndrome** on **sleep disturbances**, **depression** and **anxiety disorders** [29]. On the opposite of women life, daily lemon balm (80 mg/d) for six weeks in a formulation improved sleep quality and well-being in menopausal women [30]. Moreover, lemon balm has been tested in post-surgery patients because sleep disorders and anxiety are common, affecting more than 50% of those undergoing cardiovascular surgery [31].
In this **double-blind**, **randomized**, **placebo-controlled clinical trial**, 80 hospitalized patients who had undergone coronary artery bypass grafting were included. The treatment consisted of 500 mg capsules

of dried lemon balm leaf powder, administered three times a day for seven days, starting the day after surgery. Sleep quality and patient anxiety were assessed before and after the intervention. The results showed a **significant improvement** in both parameters. Anxiety among patients who received lemon balm, improved with an average reduction of 54.46% compared to 31.33% in the placebo group. These findings suggest a **beneficial effect** of lemon balm on **postoperative anxiety** [31].
In acute or chronic administration, the positive effects of lemon balm have been demonstrated. The effect seems to start as soon as 1h after the first intake and could also be observed after several weeks of administration without major adverse events nor tolerance issues, nor dependance. Those observations are of interest as the main medications used to treat anxiety start to be efficient after several weeks and are frequently associated with side effects [10–13].

## Mechanism of actions

In recent decades, several studies have supported the anxiolytic effects of lemon balm, deciphering its mechanism of actions.

***In vitro* studies** on rat brain, with a water or an ethanol extract of **lemon balm** showed **GABA-transaminase inhibitory activity** [32, 33]. In the first study, several plant extracts were tested with lemon balm harboring the highest effect compared to *H. perforatum* for example [32]. However, the phytochemical constituent(s) responsible for GABA-transaminase inhibition was currently unknown. Two years later, the same team of researchers isolated three active phytochemicals in lemon balm to test their effectiveness on GABA-T inhibitory activity. In the same *in vitro* model they identified **rosmarinic acid** as the main component **responsible for the inhibition of the enzyme**, with the other phytocompounds of lemon balm tested, ursolic acid or oleanolic acid contributing also to the inhibitory effect but to a lesser extend [33].
The potential **neuromodulatory effect** of lemon balm and rosmarinic acid was subsequently evaluated in another important enzyme for the central nervous system: acetylcholine esterase. The **inhibitory effect on acetylcholinesterase** was demonstrated in a time and dose-dependent manner, again, with the most potent molecule identified as rosmarinic acid [34]. This effect was also reproduced *in vivo* in animal models [35].
The monoaminergic system could also be involved in the physiopathology of anxiety disorders. The effect of lemon balm on this system was also demonstrated *in vitro* [36]. This study revealed the potential **inhibitory activity of MAO-A** by both a methanolic and aqueous extracts of lemon balm in PC-12 cell lines [36].
The radical-scavenging activity of different fractions from the crude extract of lemon balm and isolated compounds was assessed using TBARS (thiobarbituric acid reactive substances — relecting lipids peroxidation) in cerebral tissue, and DPPH assays. The hydroalcoholic extract and various fractions of

lemon balm significantly **inhibited iron-induced TBARS production** in brain preparations ($P < 0.001$), indicating strong antioxidant properties. Additionally, these extracts demonstrated **significant DPPH radical-scavenging activity** ($P < 0.001$), further supporting the potent **antioxidant potential** of lemon balm in combating oxidative stress in the brain [37].
Moreover, *Melissa officinalis* and rosmarinic acid harbor **anti-inflammatory activities** that can be useful in brain disorders. For example, in a neuroinflammatory animal model, administration of rosmarinic acid decreased the expression of pro-inflammatory genes (iNOS, TNFα, IL-1β) and alleviate depressive-like behaviors [38].
The **gut brain axis** has emerged as a **new aspect** to understand **mood disorders**. Microbiota dysbiosis associated with mood disorders has been described in the scientific literature [39]. Moreover, the effect of lemon balm on dysbiotic microbiota associated or not with mood disorders has also been identified [39, 40]. Nevertheless, the mechanism of actions and the bacteria involved in this gut brain axis associated with lemon used need further investigation.

# Conclusion

**Anxiety** and **sleep disorders** represent significant **global health concerns**, with substantial personal and societal burdens. While conventional **pharmacological treatments** exist, their long-term use is often limited by **side effects** and **dependency risks**. As such, there is growing interest in alternative and complementary therapies.

**Lemon balm**, a medicinal plant **traditionally used** for calming and sleep-inducing effects, has demonstrated notable **anxiolytic** and **sleep-improving properties** in both preclinical and clinical studies. These effects are attributed to its diverse phytochemical composition, particularly **rosmarinic acid**, which influences multiple **physiological systems** involved in **anxiety** — namely the GABAergic, cholinergic, monoaminergic systems, and oxidative stress pathways. Clinical trials further support its efficacy and safety profile in both acute and chronic administration, without major side effects.

Given these findings, **lemon balm** emerges as **a natural adjunct** to standard pharmacological approaches for **managing anxiety** and associated **sleep disorders**, warranting further exploration and integration into integrative health strategies.

## Why Groupe Berkem?

- ✓ Pioneer in plant extraction for over 60 years
- ✓ In-house manufacturer
- ✓ R&D innovation
- ✓ Ethical and premium sourcing
- ✓ Tailor-made ingredient development
- ✓ Premium nutraceutical range

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