Natural medicine compounds for anxiety, depression & mood disorders

KEY LEARNINGS

Anxiety

- Anxiety disorders are the most prevalent psychiatric disorders observed in primary care.
- Up to 90% of patients with generalised anxiety disorder also suffer from depression.
- The aetiology of psychiatric disorders is driven by a complex interplay of biological, psychological, social and environmental factors.

GABA, VOCC & Serotonin

- Anxiety and neurological disorders are often associated with dysfunctions in GABA neurotransmission.
- Elevated Ca^{2+} influx through voltage operated calcium channels (VOCC) increases the release of excitatory neurotransmitters that are implicated in many neurodegenerative diseases.
- Certain serotonin receptors regulate circadian rhythm, thermoregulation and play a role in stress related disorders, such as anxiety, insomnia and depression.

Lemon Balm

- Lemon balm has been found to inhibit GABA-T, leading to increased GABA levels in the brain.
- Certain constituents have moderate binding affinity at benzodiazepine sites, enhancing receptor sensitivity for endogenous GABA.
- Lemon balm has been investigated for a wide range of mental health conditions, including anxiety, stress, depression, sleep disorders and PMS.

Lavender

- Lavender possess analgesic, antispasmodic, antidepressant, carminative and sedative properties that may be beneficial for anxiety, depression and insomnia.
- Lavender oil modulates VOCC, reducing the expression of excitatory neurotransmitters.
- It has also shown to reduce 5-HT1A binding potential, leading to increased serotonin levels.

Skullcap

- The anti-anxiety, relaxant and antispasmodic effects chiefly correspond to flavonoids found in Skullcap.
- Baicalin and baicalein are purported to have anxiolytic effects by selectively binding to GABA-A receptor sites.
- Flavonoids have also shown binding affinity for serotonin receptors, which play a role in the regulation of circadian rhythms and mood regulation.

B6 & Zn

- Vitamin B6 plays an important role in the synthesis of serotonin, dopamine, norepinephrine, and GABA.
- Low plasma levels of B6 have been associated with depression scores.
- Zinc is involved in the regulation of dopamine transportation, and influences both GABA and glutamatergic receptors.
- Zinc deficiency can impact an individual's ability to cope with stress.

Anxiety Disorders and Comorbidities

Associated with a high burden of illness, anxiety disorders are the most prevalent psychiatric disorders observed in primary care, affecting approximately 1 in 7 Australians.[1,2] One of the most common anxiety conditions, generalised anxiety disorder (GAD) is diagnosed whereby worrying is unmanageable and causes marked impairment in work and social functioning.[3] Apart from uncontrollable worrying, somatic features such as restlessness, fatigue, concentration problems, irritability, muscle tension or sleep disturbances are often involved.[4]

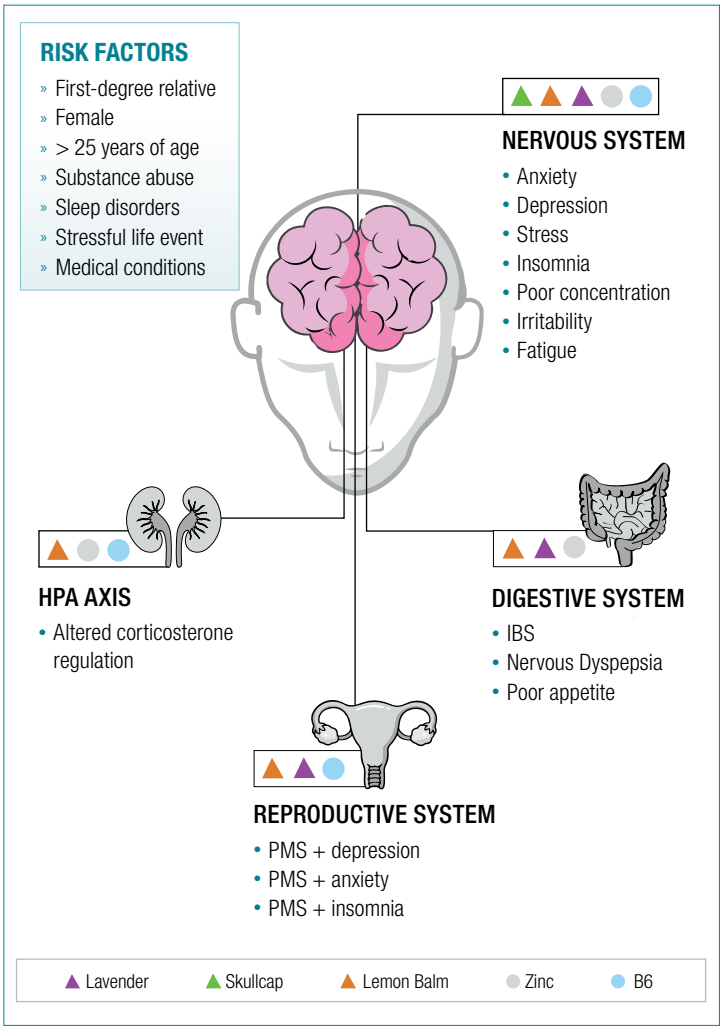
Studies indicate approximately 8 out of 10 patients with GAD will also suffer from a comorbid mood disorder within their lifetime,[5] with

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depression occurring in up to 90% of patients.[6] When combined, these two mental health conditions tend to be more severe, are harder to treat and result in more psychological, social and workplace impairments than either disorder alone.[6]

The aetiology of psychiatric disorders is driven by a complex interplay of biological, psychological, social and environmental factors. Anxiety disorders tend to run in families, with the likelihood of an anxiety disorder in a first-degree relative of an affected individual being 4 to 6 times greater than relatives of unaffected individuals.[7] Women are twice more likely than men to develop GAD, with the incidence usually occurring after 25 years of age.[8] Other risk factors also exist for the development of anxiety disorders such as a stressful life event, certain medications, medical conditions, sleep disorders, substance/alcohol abuse, and negative environmental influences.[3]

Figure 1: Anxiety disorders & comorbidities



The role of GABA, VOCC & Serotonin

Biologically, anxiety and neurological disorders, are often associated with dysfunctions in γ-Aminobutyric acid (GABA) neurotransmission.[9] GABA is considered to be the primary inhibitory neurotransmitter in the central nervous system and the spinal cord, contributing to the stability of brain activity and potentially reducing excitatory cascades.[3] GABA receptors are found in every region of the human brain and are consequently implicated in a number of processes, such as motor function, pain, sleep, and anxiety.[10]

GABA activity is mediated through GABA-A and GABA-B receptor binding, and GABA levels may be maintained by inhibiting the activity of GABA transaminase,[11] an enzyme which catabolises GABA. Consequently, modulating the GABAergic system is a logical target to prevent and treat anxiety disorders and its associated comorbidities.[11]

Under anxiety or stress conditions, it has also been postulated that elevated Ca^{2+} influx through voltage operated calcium channels (VOCC) increases the release of neurotransmitters, including glutamate and norepinephrine.[12] These excitatory neurotransmitters have been implicated in the pathophysiology of many acute and chronic neurodegenerative diseases and should additionally be considered when treating mood disorders.

Serotonin is a major neurotransmitter that exerts its diverse physiological effects through various receptor subtypes, including 5-HT7. Found in high concentrations in the hypothalamus, thalamus, hippocampus, brainstem and cortex, accumulating evidence suggests this receptor regulates circadian rhythm, thermoregulation and plays a role in stress related disorders, such as anxiety, insomnia and depression.[13] Abnormalities in receptor functions due to decreased receptor affinity to neurotransmitters or decreased numbers, have also been linked to behavioural and somatic symptoms often seen in depression, such as changes in sleep, appetite and pain.[14]

Melissa officinalis (Lemon Balm)

A member of the Lamiaceae family, *Melissa officinalis* is indigenous to southern Europe and the Mediterranean and is traditionally considered a tonic for the nervous system.[15] Its anti-inflammatory, antioxidant, sedative and neuroprotective actions have been associated with the phenolic and flavonoid constituents, namely rosmarinic acid, ursolic acid and oleanolic acid.[16] These compounds have been found to inhibit the enzyme GABA-T, leading to increased GABA levels in the brain and potentially influencing anxiety.[9] Additional in-vitro investigations have observed certain constituents found in the leaves of *Melissa officinalis* to have moderate binding affinity at the benzodiazepine site, enhancing receptor sensitivity for endogenous GABA.[17]

Murine models have shown the ability of *Melissa officinalis* to reduce serum corticosterone levels, potentially contributing to the reduction in anxiety behaviours, increased cell proliferation and neuroblast differentiation noted in studies.[18] Constituents found in Lemon balm may also contribute to neural protection due to their role in free radical scavenging and protection against hydrogen peroxide induced neuronal damage, indicating its usefulness in central nervous system disorders.[19]

Clinical Data

In human trials, *Melissa officinalis* has been investigated for a wide range of mental health conditions, including anxiety, stress, depression and sleep disorders. In an 8-week double-blind, placebo-controlled clinical trial, patients receiving 3g/day of *Melissa officinalis* experienced significant reductions in depression, anxiety, stress and total sleep disturbance compared to placebo ($P < 0.05$).[20] The antidepressant activity of *Melissa officinalis* was assessed in an 8-week double-blind,

Table 1: Herbal and nutritional mechanisms in managing mood disorders

Natural Medicine	Lemon balm	Skullcap	Lavender	B6	Zinc
Action	Inhibits GABA-T; Binds to benzodiazepine receptor sites.	Binds to GABA-A/ Benzodiazepine receptor sites; Has affinity for 5-HT7 receptors.	Modulates VOOC; Reduces 5-HT1A binding potential.	Cofactor for neurotransmitters; Calcium channel blocking activity.	Cofactor for neurotransmitters; Modulates NMDA receptor activity.
Potential Use	Anxiety disorders; Stress; Insomnia; PMS; Cognitive function; Depression; Irritability; IBS; Nervous dyspepsia.	Anxiety disorders; Nervous exhaustion; Depression; Insomnia; Restlessness; Irritability.	Anxiety disorders; Stress; Insomnia; Depression; Concentration; PMS; IBS; Nervous dyspepsia; Headache.	Anxiety disorders; Stress; Irritability; Depression; PND; Addictions; Appetite; Cognition; Motivation; Healthy methylation; Pyrrole disorder; PMS.	Anxiety disorders; Stress; Depression; PND; Addictions; Appetite; Pyrrole disorder; Cognition; Agitation.

randomised pilot study assessing its efficacy compared to fluoxetine in 45 adults with mild to moderate depression.[21] Results indicated *Melissa officinalis* was equal to fluoxetine without adverse effects associated with the anti-depressant, including insomnia, headache, anxiety and increased appetite. Furthermore, a double-blind RCT found significant reductions in physical, psychological and social symptoms associated with premenstrual syndrome (PMS) in 100 school-aged females taking 1.2g of *Melissa officinalis* for three months.[22] These results were also confirmed in a randomised clinical study, which found 1.2g of Lemon balm taken in the first 7 days of the menstrual cycle reduced depression ($p = 0.001$), social disturbances ($p = 0.021$), anxiety and sleep disturbances ($P < 0.001$) in 100 females with PMS.[23]

Scutellaria lateriflora (Skullcap)

Native to America and Europe, Skullcap *(Scutellaria lateriflora)* has been used in traditional herbal medicine to support individuals during times of nervousness.[24] The anti-anxiety, relaxant and antispasmodic effects chiefly correspond to a number of flavonoids found in the dried aerial parts of the herb.[10] In preclinical studies, isolated baicalin and baicalein compounds are purported to be involved in the anxiolytic effects by selectively binding to GABA-A receptor sites.[25] In animal models, this selective binding demonstrated reductions in nervousness without the cognitive impairment and motor incoordination that can occur alongside other GABA-A modulators.[26] Specific flavonoids have also been shown to have an affinity to the benzodiazepine site of GABA-A receptors, decreasing the action of excitatory neurotransmitters and thus exhibiting an anxiolytic response. In addition, flavonoids from *Scutellaria lateriflora* have shown binding affinity for serotonin receptors in-vitro, specifically 5-HT7 receptors.[27] In the hypothalamus, it is believed to play a role in the regulation of circadian rhythms and endocrine function, while thalamic and cortical 5-HT7 receptors may influence mood regulation. In animal models, baicalin has shown to produce an antidepressant effect by inhibiting monoamine oxidase A + B and reducing markers of neuroinflammation, including cyclooxygenase-2 and prostaglandin E2 in the frontal cortex and hippocampus.[28,29]

Clinical data

The antidepressant and anxiolytic actions of *Scutellaria lateriflora* have been observed in 2 human trials. A randomised, double-blind placebo-controlled crossover study reported significantly enhanced mood without compromising energy or cognition after 2 weeks of Skullcap administration at 350mg, three times a day.[30] An additional double-bind, crossover, randomised controlled trial found a reduction in anxiety and stress in 19 volunteers taking various doses of *Scutellaria lateriflora* (100mg, 200mg and 350mg).[31] Although all three preparations demonstrated a clinical anxiolytic effect, statistical data was not reported, indicating the need for higher quality studies to enable clear conclusions on the effects of *Scutellaria lateriflora*.

Lavandula angustifolia (Lavender)

The essential oil extracted from the flowers of *Lavandula angustifolia* have been used in folk and traditional medicine for a wide range of conditions owing to its analgesic, antidepressant, antispasmodic, carminative and sedative properties.[32] Linalool, linalyl acetate, 1.8-cineole, β-ocimene, terpinene-4-ol and camphor are the main constituents found to have therapeutic benefits both topically and orally.[33]

The oral ingestion of lavender oil may work by a different mechanism to that seen in inhalation studies. While researchers initially postulated that lavender oil may affect neurotransmitter targets such as GABA-A, monoamine-oxidase-A or N-methyl-D-aspartate receptors to produce its calming effects, modulation of voltage operated calcium channels (VOCC) by lavender oil has also been demonstrated.[34] Elevated calcium channel activity can contribute to increased release of neurotransmitters, including glutamate and norepinephrine, leading to inadequate stress response of the central nervous system. The precise mechanism by which lavender oil causes this modulation has not been defined, though it has been proposed either direct or indirect binding with calcium channel complexes causes inhibition.[34] Furthermore, lavender oil has been shown to reduce 5-HT1A binding potential leading to increased serotonin levels, and the inhibitory effect of linalool on glutamate binding has been reported in rat models, suggesting the sedative effects may be mediated through this transmission.[35,36]

The mechanism by which lavender oil may support sleep is currently being investigated. In one animal study, female NMRI mice received an oral dose of 1–30mg/kg of an essential oil of *Lavandula angustifolia* flowers, containing linalool at 36.8% and linalyl acetate at 34.2%. A potentiation of pentobarbital sleep time was observed and in contrast

to being a direct sedative, researchers postulated that lavender oil worked as a sleep promoter.[34] As disturbed sleep has been identified as a comorbidity of anxiety, *Lavandula angustifolia* may pose a therapeutic benefit in anxiety-related insomnia.

Clinical data

In three human clinical trials, an oral lavender oil preparation (essential oil produced from lavender flowers by steam distillation) at a daily dose of 80mg/day, showed efficacy in mixed anxiety disorders, generalised anxiety disorders, as well as restlessness and agitation.[37-39] This preparation showed superiority over placebo in 221 adults with mixed anxiety disorders,[37] and similarly, it was as efficacious and better tolerated than 0.5mg/day of paroxetine in a trial consisting of 539 patients with generalised anxiety disorder.[38] Lavender oil was also demonstrated to improve sleep, mood, general well-being and quality of life in patients with neurasthenia and PTSD [40] and displayed pronounced calming effects without sedation in patients with restlessness and disturbed sleep.[39]

B6

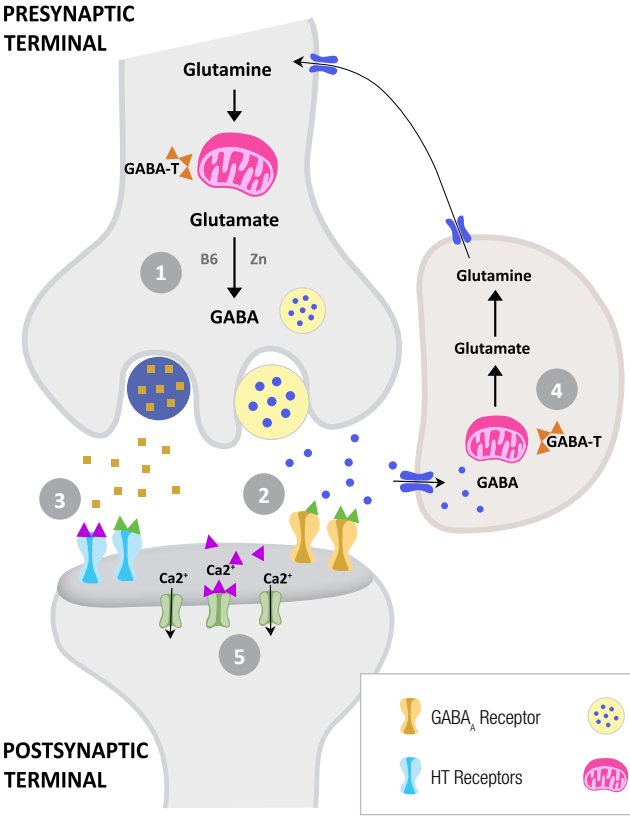
As a crucial enzymatic cofactor, vitamin B6 plays an important role in the synthesis of serotonin, dopamine, norepinephrine, and GABA in brain and nerve cells and may support healthy mood and nerve conduction.[41] Pyridoxine deficiency tends to selectively reduce the brains production of serotonin and GABA, and consequently can exacerbate dysphoric states.[42] Low plasma levels of B6 have been associated with depression scores and higher intakes are correlated with lower rates of depression, reinforcing its mood enhancing activity.[43]

High concentrations or prolonged stimulation of glutamate may also cause a huge influx of Ca^{2+} into the neurons, which has been implicated in the pathophysiology of many acute and chronic neurodegenerative diseases.[44] Pyridoxine has been shown to possess calcium channel blocking activity thereby exhibiting a protective role against glutamate-induced neurotoxicity. Furthermore, vitamin B6 favourably effects anxiety and stress by downregulating glucocorticoid receptor activity and reducing sympathetic output, thus blunting the physiological impact of corticosteroids.[42]

Zinc

Known to play a pivotal role in neural development and mood disorders, zinc is found primarily in the regions of the brain involved in emotions such as the hippocampus, frontal cortex, amygdala and olfactory bulb.[45] In the central nervous system, zinc plays an important role in neurotransmitter synthesis where it is involved in the regulation of dopamine transportation, and influences both GABA and glutamatergic receptors.[46] Decreased zinc levels have been shown to contribute to alterations in behaviour and abnormal neurological development as a direct result of increased glucocorticoid secretion.[45,47] Under dietary zinc deficiency, glucocorticoids target the hippocampus where their action is associated with disturbances of glutamatergic neurotransmission, which may lead to depressive symptoms and aggressive behaviour.[47] Zinc may also modulate activity of the N-methyl-D-aspartate (NMDA) receptor, whose excessive activation has been associated with the pathophysiology of depression and mood disorders.[45] Zinc deficiency can, therefore, impact an individual's ability to cope with stress and may influence the development of mood disorders.

Figure 2: Herbs and nutrients which attenuate the pathology of anxiety disorders



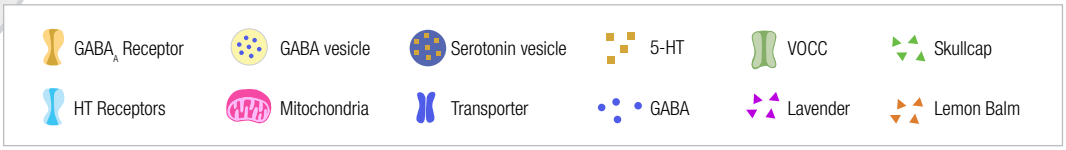
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2 GABA receptors are found in every region of the human brain and are consequently implicated in a number of processes, such as motor function, pain, sleep, and anxiety.[10] The flavonoid baicalin found in Skullcap has been shown to be a partial agonist of GABA-A receptors, decreasing the action of excitatory neurotransmitters.

3 Serotonin is a major neurotransmitter that exerts its diverse physiological effects through various receptor subtypes. Flavonoids found in Skullcap have demonstrated binding affinity to 5-HT7 receptors. These receptors may regulate circadian rhythm, thermoregulation, and play a role in stress related disorders, such as anxiety, insomnia and depression.[13] Lavender oil may also reduce 5-HT1A binding potential, leading to increased serotonin levels.

4 GABA levels may be maintained by inhibiting the activity of GABA transaminase,[11] an enzyme which catabolises GABA. Phenolic and flavonoid compounds found in Lemon balm have found to inhibit this enzyme, leading to increased GABA levels in the brain and potentially influencing anxiety.[9]

5 Under anxiety or stress conditions, it is postulated that elevated Ca2+ influx through voltage operated calcium channels (VOCC) increases the release of neurotransmitters, including glutamate and norepinephrine.[12] Lavender oil has been proposed to modulate VOCC, reducing the expression of these excitatory neurotransmitters.



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