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- **Pregnancy May End with Delivery. Our Care Shouldn't.**
- **Over-the-Counter Plant-Derived Agents for Anxiety Disorders: An Evidence-Informed Narrative Review of 10 Agents**
- **Probable Behavioral Variant Frontotemporal Dementia in a 33-Year-Old: A Case Report and Review of Early-Onset Presentations**

Editorial Board

The Journal of *Medical Advancements and Research*

Articles:

Pregnancy May End with Delivery. Our Care Shouldn't.

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CONFLICTS OF INTEREST STATEMENT

Dr. Glenn reported the following disclosures: speaker for Alkermes and Advisory Board for Bristol Myers Squibb. Dr. Buschjost does not have any conflicts of interest to report regarding this op-med.

ABSTRACT

This op-med focuses on the importance of management of women's health across the lifespan.

Keywords: post-partum, weight management, women's mental health, hormones

A colleague asked me the other day about my patient demographics. My response is the same, whether I'm discussing my psychiatry clinic, weight management clinic, or psychiatry weight management clinic—middle aged moms. In my clinics, I care for women struggling with depression, obesity, or both. No matter which clinic I'm in, I hear the same story: many trace the beginning of their struggles back to the postpartum period.

The journey through pregnancy is not easy, and for some, their mental and physical health take a huge hit. Following delivery, the first six weeks of postpartum are often filled with sleepless nights, pain, a hormonal tsunami, and a body we don't even recognize anymore. Magically, at our 6–8-week post-delivery follow up, if baby is okay, mom is okay…right? Not quite.

We ask women to recover from one of the biggest physiologic events of their lives while functioning on fragmented sleep, learning to care for an infant, returning to work, and somehow finding time to care for themselves. Each of these factors are both cause and consequence of the others. A night of fragmented sleep and the demands of infant care leave a new mother more vulnerable to low mood, more likely to reach for convenient and calorie-dense foods, and less able to engage in physical activity. Poorer nutrition and inactivity, in turn, worsen sleep quality and depressive symptoms, further eroding the capacity for self-care. What results is a tightly woven system in which any single disruption reverberates across all domains, and in which all of them directly influence a woman's ability to maintain their physical and mental health.

This isn't simply a matter of willpower. Estrogen and progesterone fall dramatically after delivery. Appetite regulation shifts. Sleep deprivation alters hunger hormones. Breastfeeding changes energy demands. The body is undergoing enormous physiologic adaptation at the very time society expects women to "bounce back."

Who should be caring for these women? Every specialty sees a different piece of the puzzle. Obstetricians guide women through pregnancy and delivery. Primary care manages chronic disease. Obesity medicine addresses metabolic health. Psychiatry helps women navigate depression, trauma, anxiety, and increasingly recognizes how mental and physical health intersect during the postpartum period. Yet no single specialty owns postpartum recovery, leaving many women navigating these transitions alone. Instead of one coordinated plan, mothers are left to navigate disconnected appointments, fragmented advice, and the expectation that they will somehow put the pieces together themselves.

Where does this leave us? As a health system, we have become siloed to the point of patients falling through the cracks, particularly our postpartum moms. We need a system in place that allows for interdisciplinary collaboration to focus on the whole person, not individual symptoms. Not only do we need a team comprised of experts in hormonal fluctuations, nutrition, physical activity, mental health, and medication management across the postpartum experience, but we need a team that can communicate with each other across the spectrum. Maternal healthcare shouldn't be a relay race where each specialty hands off the baton. It should be a team sport.

New motherhood changes priorities in beautiful ways. Suddenly every decision revolves around someone else's needs. Meals become rushed. Sleep becomes optional. Exercise becomes a luxury. Medical appointments are scheduled for the baby, not for you. Somewhere along the way, caring for yourself begins to feel selfish when, in reality, it has never been more essential.

Taking care of yourself is not “self-care.” It is health care. It is vital for success not only for the mom, but for her relationships, her family, and her entire life. A healthy mother helps build a healthier family, not because of guilt but because of empowerment. An empowered mother raises empowered children who learn to care for their own mental and physical health.

We need to stop treating postpartum recovery as a six-week event. Instead, we should recognize it as a continuum requiring collaboration among obstetrics, primary care, psychiatry, obesity medicine, and other clinicians invested in women's long-term health. Pregnancy may end with delivery, but postpartum recovery continues long after the baby leaves the nursery. Our healthcare system should too.

Review

Over-the-Counter Plant-Derived Agents for Anxiety Disorders- An Evidence-Informed Narrative Review of 10 Agents

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CONFLICTS OF INTEREST STATEMENT

The above author does not have any conflicts of interest to report regarding this editorial.

ABSTRACT

Background: Anxiety disorders are the most prevalent mental health conditions worldwide and contribute substantially to disability and reduced quality of life. Although first-line treatments such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and psychotherapy are effective for many individuals, a significant proportion of patients seek complementary and alternative medicine (CAM) approaches, including over-the-counter plant-derived products. Clinicians are therefore increasingly likely to encounter patients using herbal agents for anxiety-related symptoms.

Methods: A narrative review of the literature was conducted using PubMed to identify plant-derived compounds evaluated for anxiety disorders and anxiety-related outcomes. Searches were limited to publications from the past 20 years and prioritized randomized controlled trials, systematic reviews, and meta-analyses. Following screening and application of inclusion and exclusion criteria, ten commonly studied plant-derived agents were selected for detailed review: ashwagandha (*Withania somnifera*), cannabidiol (CBD), chamomile (*Matricaria chamomilla*), Galphimia glauca, kava (*Piper methysticum*), lavender (*Lavandula angustifolia*), passionflower (*Passiflora incarnata*), rosemary (*Rosmarinus officinalis*), saffron (*Crocus sativus*), and St. John's wort (*Hypericum perforatum*). Evidence regarding mechanisms of action, efficacy, adverse effects, and clinically relevant drug interactions was synthesized narratively.

Results: Evidence supporting anxiolytic efficacy varied considerably across agents. Lavender (particularly standardized Silexan® preparations) and ashwagandha often appear to demonstrate the most consistent evidence for reducing anxiety symptoms and are among the few agents provisionally recommended by the World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT). Some evidence also supports saffron, CBD, passionflower, and *Galphimia glauca*, though findings appear limited by heterogeneity in study design, dosing, and product standardization. Chamomile demonstrated modest benefits but mixed long-term outcomes. Rosemary showed preliminary promise but lacks sufficient high-quality evidence. Kava demonstrated short-term anxiolytic effects but remains limited by concerns regarding hepatotoxicity and drug interactions. St. John's wort showed limited evidence for primary anxiety disorders despite previously reported evidence in depression. Many agents exhibited potential cytochrome P450-mediated interactions and other clinically relevant safety considerations.

Conclusions: Several over-the-counter plant-derived agents demonstrate potential utility as adjunctive interventions for anxiety symptoms, though the quality and consistency of evidence remain variable. Lavender and ashwagandha currently possess the strongest evidence base among reviewed agents. Limitations across the literature include heterogeneous formulations, inconsistent dosing strategies, small sample sizes, and inadequate long-term safety data. These products should not replace established first-line treatments but may serve as potential options when used with appropriate clinical oversight. Greater standardization and higher-quality trials are needed to clarify their role in the management of anxiety disorders.

Keywords: Anxiety disorders, Phytotherapy, Phytoceutical, Herbal medicine, Dietary supplements, Complementary and alternative medicine, Neuropharmacology, Botanicals

Introduction

In 2019, mental disorders remained among the top ten leading causes of global disease burden after conducting a study of 204 countries and territories across a time line of nearly 3 decades. Among these, anxiety disorders – encompassing all associated subtypes – were demonstrated to have contributed the most in terms of prevalence, from an estimated 194.9 million in 1990 to 301.4 in 2019, and contributing substantially to disability-adjusted life-years (GBD 2019 Mental Disorders Collaborators, 2022). Complementing these figures, the World Health Organization identifies anxiety disorders as the most common mental disorder globally, affecting 359 million individuals as of 2021. Anxiety disorders frequently emerge in childhood and adolescence, disproportionately affect women, and remain undertreated – with only approximately 1 in 4 affected individuals receiving care (World Health Organization [WHO], 2023).

Anxiety disorders encompass several diagnoses including specific phobias, social anxiety disorder, generalized anxiety disorder, panic disorder, and agoraphobia (Penninx et al., 2021). While obsessive–compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) were historically classified within anxiety disorders in the DSM-IV, the DSM-V reclassified these conditions into separate chapters; though they were placed adjacent to reflect a deep connection (Ren et al., 2023). Of those with anxiety disorders, comorbidity is high, with approximately half to 2/3 of adults with anxiety struggling with a comorbid diagnosis of depression. Treatment of anxiety disorders is low, with both low-income and high-income countries struggling to adequately provide care (Penninx et al., 2021)

Pharmacologic treatments for anxiety disorders are well established, with first-line options including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) based on their overall risk–benefit profiles. Additional pharmacologic strategies may include tricyclic antidepressants, benzodiazepines, gabapentinoids, buspirone, mirtazapine, and, in selected cases, antipsychotic agents (Bandelow et al., 2017). Many patients may remain symptomatic despite several treatments, including multiple trials and combinations of drugs. Side effects and cost may also cause issues with noncompliance as well (Ravindran & da Silva, 2013).

In this context, many individuals seek complementary and alternative medicine (CAM) approaches to address anxiety-related symptoms, manage chronic illness, or mitigate side effects associated with conventional pharmacotherapy. CAM practices are often perceived as aligning aligning greater with holistic health philosophy, transformational experiences, and as a way of gaining control over one's own health (Bandelow et al., 2017). These interventions encompass a wide range of modalities, including physical therapies such as acupuncture, nutraceuticals (e.g., dietary supplements, vitamins, and minerals), and herbal remedies, also referred to as phytoceuticals (e.g., plant-derived or plant-extracted natural products) (Bandelow et al., 2017; Sarris et al., 2022).

Importantly, many patients utilize CAM approaches to complement conventional care rather than as an alternative – raising clinically relevant concerns regarding potential drug–drug interactions and safety considerations (Bandelow et al., 2017). Data from the 2007 National Health Interview Survey (NHIS) indicated that 40% of adults had been using some form of CAM (Lind et al.,

2010). Despite widespread use, many individuals engage in these practices without medical supervision, and clinician familiarity with CAM agents remains variable (Ravindran & da Silva, 2013). This disconnect highlights the need for clinicians to understand both the potential benefits and risks associated with commonly used over-the-counter interventions.

A growing body of research has evaluated the use of plant-derived compounds and herbal preparations for anxiety-related outcomes, including randomized controlled trials on individual agents. However the existing literature is often heterogenous – and often difficult to interpret given inconsistent dosing, outcome measures, and diagnostic specificity. While some agents may be thought to provide benefits that may outweigh side effects of many typically utilized medication, others such as St. John's Wort have been associated with harmful effects such as inducing mania (Sarris et al., 2011).

This present narrative review aims to provide an evidence-informed synthesis of plant-derived agents used over the counter for anxiety disorders as defined by DSM-5 criteria with attention to anxiolytic efficacy, proposed mechanism of action, clinically relevant safety considerations, including adverse effects and potential drug-drug interactions. Of note, this study does not recommend the use of these agents as primary treatment for anxiety disorders, but rather seeks to synthesize information in such a way to facilitate communication between patients and their providers – in order to formulate treatment plans and build rapport with patients that may seek to utilize these treatments as ways to alleviate their symptomatic burden.

Methods

A literature search was conducted in PubMed to identify studies evaluating herbal, plant-derived compounds for the treatment of anxiety disorders. The search was limited to publications from the past 20 years to reflect contemporary diagnostic frameworks, outcome measures, and clinical relevance. To enhance methodological rigor while maintaining feasibility within a narrative review framework, search results were further restricted to randomized controlled trials, meta-analyses, and systematic reviews.

The following Boolean search strategy was employed: ("separation anxiety" OR "selective mutism" OR "specific phobia" OR "social anxiety" OR "performance anxiety" OR "panic disorder" OR "panic attack" OR "agoraphobia" OR "generalised anxiety" OR "generalized anxiety") AND ("over-the-counter" OR "OTC" OR herbal* OR nutra* OR supplement* OR nootropic* OR adaptogen* OR phyto*).

The search strategy was restricted to anxiety disorders as classified in the DSM-5. Obsessive–compulsive disorder was considered but excluded to maintain diagnostic consistency and avoid conceptual overlap with disorders no longer categorized under anxiety disorders in current nosology. Non-specific diagnostic categories – including anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder – were often excluded due to diagnostic heterogeneity and limited interpretability across studies; except where outside of this framework data was limited. When anxiety measures were used across multiple studies, including within select populations, specific pathologies, or surgical interventions, these studies were at times included due to notable trends observed in the findings.

The initial search yielded 132 records. All studies were screened at the title and abstract level, followed by full-text review when indicated. Studies were evaluated for explicit investigation of named herbal agents derived from plant sources and assessed for anxiety-related outcomes.

The primary objective of this initial search phase was not to evaluate comparative efficacy, but rather to identify plant-derived compounds most commonly examined in the literature for anxiety treatment. From this process, a consolidated list of frequently referenced herbal agents was generated.

Several exclusion criteria were applied to preserve interpretability and agent-specific relevance:

1. Combination herbal products (e.g., *Shugan Jieyu*, *Manasamitra Vataka*, or formulations combining multiple botanicals and minerals such as *Crataegus oxyacantha*, *Eschscholzia californica*, and magnesium) were excluded, as these formulations precluded attribution of observed effects to a single active agent.
2. Nutraceuticals and non-herbal compounds were excluded despite inclusion in the initial search strategy. This decision was made to maintain a focused review of plant-derived compounds and to allow for a more coherent synthesis of phytochemical mechanisms and clinical data.
3. Studies that referenced interventions using overly broad or non-specific terminology (e.g., "herbal medicine" or "traditional formulations") without naming individual plant-based agents were excluded.
4. Studies that did not target anxiety disorders or measure anxiety symptoms as a primary outcome were excluded.
5. Additional plant-derived compounds were excluded when the available literature did not primarily examine anxiety outcomes. This included botanicals with limited anxiety-specific evidence (e.g., blueberries), compounds primarily studied for cognitive enhancement with secondary effects on anxiety (e.g., *Bacopa monnieri*, *Ginkgo biloba*), and agents whose primary clinical focus was sleep promotion rather than anxiolysis (e.g., *Valeriana officinalis*).

A systematic review following PRISMA guidelines was not conducted, as the primary aim of this review was to identify and characterize herbal agents most commonly examined for anxiety disorders rather than to evaluate comparative efficacy or generate pooled effect estimates. Given the substantial heterogeneity across anxiety diagnoses, outcome measures, herbal preparations, and dosing strategies, a narrative review approach was deemed more appropriate to contextualize the existing literature and guide subsequent agent-specific analysis.

Using this approach, the following herbal compounds were most consistently identified in the literature as treatments for anxiety disorders:

- Ashwagandha (*Withania somnifera*)
- Cannabidiol (CBD)
- Chamomile (*Matricaria chamomilla*)
- *Galphimia glauca*
- Kava (*Piper methysticum*)

- Lavender (*Lavandula angustifolia*)
- Passionflower (*Passiflora incarnata*)
- Rosemary (*Rosmarinus officinalis*)
- Saffron (*Crocus sativus*)
- St. John's wort (*Hypericum perforatum*)
-

These agents formed the basis for subsequent narrative synthesis and discussion. For each identified herbal agent, focused literature searches were conducted to characterize proposed mechanisms of action, clinical efficacy, and safety considerations. These searches prioritized randomized controlled trials, meta-analyses, and systematic reviews, with additional reference to mechanistic and pharmacologic studies when necessary to contextualize clinical findings. To provide a contextual framework for interpreting our findings, results from the present literature review will be compared, when applicable, with the *Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* developed by the World Federation of Societies of Biological Psychiatry and the Canadian Network for Mood and Anxiety Treatments Taskforce, as these guidelines represent a recent effort to assist clinicians in evaluating the efficacy of herbal (phytoceutical) interventions (Sarris et al., 2022).

Information extracted for each agent included botanical source, proposed neurobiological mechanisms, anxiety-related outcomes, dosing ranges where available, adverse effects, and clinically relevant drug–herb interactions. Findings were synthesized narratively to highlight areas of consensus, variability, and limitation within the existing literature rather than to generate pooled effect estimates.

Results (Agent by Agent Review)

Ashwagandha (*Withania somnifera*)

Ashwagandha (*Withania somnifera*) is a small shrub native to arid regions of South and Central Asia, Africa, the Middle East, the Canary Islands, and the Mediterranean basin (Lopresti et al., 2019; Speers et al., 2021). It has been used for millennia within Ayurveda, an ancient system of medicine originating in India over 3,000 years ago, and is known by several regional names including Asand (Urdu), Indian winter cherry, and poison gooseberry (Alsanie et al., 2026; Majeed et al., 2023; Speers et al., 2021). *Withania somnifera* has been incorporated into more than 100 traditional formulations, with historical applications spanning inflammatory conditions, respiratory disease, endocrine disorders, gastrointestinal complaints, and neuropsychiatric indications such as anxiety, insomnia, and neurological disorders (Speers et al., 2021). As of 2019, it ranked as the fifth most commonly used dietary supplement in the United States (Lopresti et al., 2019).

Approximately 140 specialized metabolites have been identified within *Withania somnifera*. The principal bioactive compounds consist of steroidal alkaloids and lactones collectively referred to as withanolides. Several withanolides contain electrophilic moieties capable of thiol reactivity, a property thought to contribute to their biological activity, including antioxidant effects and modulation of transcriptional or post-transcriptional signaling pathways via interactions with electrophile-sensitive cellular targets (Speers et al., 2021).

Withania somnifera is commonly classified as an adaptogen, defined as an agent that promotes systemic homeostasis through multimodal, non-specific mechanisms rather than through a single pharmacologic target. Proposed mechanisms of action include attenuation of hypothalamic–pituitary–adrenal (HPA) axis and sympathetic–adrenal–medullary (SAM) axis activation, antioxidant and anti-inflammatory effects, GABAergic modulation, immune regulation, serotonergic activity, and chronomodulatory effects on sleep–wake regulation (Speers et al., 2021; Jamnekar et al., 2025).

Clinical evidence supporting anxiolytic and stress-reducing effects includes a randomized controlled trial in which 240 mg daily of a standardized (2.5% withanolides) *Withania somnifera* extract (Shoden®), administered for 60 days, resulted in a mean cortisol reduction of approximately 23%, with no significant change observed in the placebo group (Lopresti et al., 2019). Similarly, lower salivary cortisol levels, higher urinary serotonin concentrations, and significant reductions in GAD-7 and Perceived Stress Scale scores were observed in a study of 54 individuals receiving ashwagandha root extract 500 mg daily combined with 5 mg of piperine (95% standardized extract) for 60 days (Majeed et al., 2023). Comparable findings were reported in a 2025 study by Majeed et al., demonstrating significant reductions in Hamilton Anxiety Rating Scale (HAM-A) scores at days 30, 60, and 90 compared with placebo.

A systematic review of 14 clinical studies demonstrated overall support for the use of *Withania somnifera* in reducing stress and anxiety symptoms and improving sleep quality when administered for durations of two months or longer (Marchi et al., 2025). The methodological strength of this review was attributed to the inclusion of exclusively double-blind, placebo-controlled trials; however, limitations included inconsistent reporting of blinding procedures, heterogeneity in study populations, variability in extract formulations, and insufficient evaluation of compound-specific bioavailability. Pratte et al. (2014), in a systematic review of five trials, similarly observed improvements in anxiety and stress scales but emphasized caution due to methodological variability and potential bias. A systematic review and meta-analysis of nine studies (n = 558) demonstrated statistically significant reductions in perceived stress, anxiety, and serum cortisol levels, though variability in formulation, treatment duration, and dosing prompted calls for further standardization (Arumugam et al., 2024). Another systematic review of five RCTs reported reductions in HAM-A scores (MD = −5.06) while noting the need for larger sample sizes to strengthen conclusions (Fatima et al., 2024). Alsanie et al. (2026) additionally reviewed 22 studies, reporting decreases in stress, depression, and anxiety – though noted a need to address heterogeneity between studies, as well as define time frame and optimal dose.

From a safety standpoint, *Withania somnifera* has generally been well tolerated. Reported adverse effects are typically mild to moderate and transient, including somnolence, dizziness, vertigo, and drowsiness (Speers et al., 2021). In a study of healthy volunteers, administration of 300 mg daily of KSM-66® ashwagandha root extract for eight weeks was not associated with clinically significant changes in liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase), hematologic parameters (hemoglobin, platelet count, neutrophil count), or thyroid function, and no adverse events were reported (Verma et al., 2021). Preclinical toxicology studies similarly demonstrated no evidence of toxicity or pathological changes in pregnant rats or fetuses exposed to doses of 2,000 mg/kg or greater (Speers et al., 2021).

Although overall toxicity concerns appear limited, potential herb–drug interactions warrant consideration. Available data remain somewhat limited in clinical relevance and require further clarification. In one study evaluating four ashwagandha extracts (root and leaf), no reversible inhibition (IC_{50} > 100 µg/mL) was observed across CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, and CYP2B6 recombinant enzymes (Raichura et al., 2025). Similarly, crude extracts and isolated phytoconstituents did not demonstrate significant inhibition of CYP3A4 or CYP2D6 activity in human liver microsomes (Savai et al., 2015). However, methanolic and ethyl acetate extracts were shown to inhibit CYP2B6 (IC_{50} values of 79.16 µg/mL and 57.96 µg/mL, respectively) and were characterized as moderate inducers of CYP3A4 (Kumar et al., 2021). Withanone, a withanolide associated with potential cognitive benefits, did not exhibit significant inhibition of major CYP isoenzymes but was found to be extensively metabolized by CYP3A4 and CYP1A2 (Singh et al., 2021). Given variability across extraction methods and formulations, Dipankar et al. (2025) suggested monitoring medications metabolized by CYP3A4 and CYP2D6 (e.g., warfarin, digoxin, SSRIs), as well as exercising caution with immunosuppressive agents due to potential immunomodulatory effects and additive sedation when combined with other sedative medications.

According to the *Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* issued by the WFSBP and CANMAT Taskforce, *Withania somnifera* is provisionally recommended as monotherapy for anxiety disorders (Sarris et al, 2022). Within these guidelines, lavender is the only other herbal intervention to receive a comparable recommendation. Taken together, ashwagandha appears best positioned as a potential intervention for patients with mild to moderate anxiety symptoms, particularly when stress, sleep disturbance, or HPA-axis dysregulation are prominent. While evidence supports modest efficacy and favorable tolerability, variability in extract formulation and dosing limits broad generalizability. Its use should therefore complement, rather than replace, established first-line treatments.

Cannibidiol (CBD)

Cannabidiol (CBD) is an over-the-counter compound that is additionally approved by the U.S. Food and Drug Administration for the treatment of Lennox–Gastaut syndrome and Dravet syndrome in the form of Epidiolex® (Skelley et al., 2020). CBD is a phytocannabinoid constituent of *Cannabis sativa* and *Cannabis indica*, species within the *Cannabis* genus of flowering plants, which are among the most commonly used recreational substances in the Western Hemisphere (Blessing et al., 2015; Gobbi et al., 2019). The primary psychoactive cannabinoid in the cannabis plant is Δ^9-tetrahydrocannabinol (THC), which mediates most psychoactive and mood-altering effects and possesses addictive properties (Gobbi et al., 2019). The psychotropic effects of THC are largely attributed to its binding and activation of G-protein–coupled cannabinoid receptors (CB1 and CB2) (Izzo et al., 2009).

However, the endocannabinoid system as a whole may offer therapeutic value beyond cannabis's recreational use. This system has been shown to modulate several physiological and pathophysiological processes, including neurotransmitter release in the central and peripheral nervous systems, pain perception, immune signaling, and gastrointestinal and hepatic function (Izzo et al., 2009; Skelley et al., 2020).

CBD in particular has been proposed to exert multiple beneficial pharmacological effects and has been investigated as a potential therapeutic agent for inflammation, diabetes, cancer, and affective or neurodegenerative disorders (Izzo et al., 2009). CBD has been characterized as having a diverse array of mechanisms, including antagonism or inverse agonism at CB1 and CB2 receptors, negative allosteric modulation of CB1 receptors, and weak inhibition of fatty acid amide hydrolase (FAAH) (Bilbao & Spanagel, 2022; Izzo et al., 2009). FAAH inhibition has been proposed to confer benefits in gut inflammation and to assist in preventing the degradation of anandamide, which has been theorized to contribute to potential anxiolytic effects (Izzo et al., 2009; Kwee et al., 2023). Additionally, CBD interactions with the 5-HT1A receptor and the transient receptor potential vanilloid 1 receptor have been associated with anxiolytic, anti-inflammatory, and neuroprotective effects (Izzo et al., 2009). Collectively, these findings suggest a complex pharmacological profile through which CBD may modulate behavior and affective states via multiple pathways.

Regarding pharmacokinetic interactions, CBD is primarily metabolized by cytochrome P450 enzymes CYP2C19 and CYP3A4 (Devinsky et al., 2018). CBD has also been implicated in the inhibition of CYP2C19, CYP3A4, and CYP2D6 (Devinsky et al., 2018; Skelley et al., 2020). Several studies have demonstrated significant increases in levels of the active metabolite of clobazam, N-desmethylclobazam, when co-administered with CBD. While one study examining pediatric patients with Dravet syndrome did not observe significant changes in antiepileptic drug (AED) levels—including valproate, topiramate, stiripentol, or levetiracetam—other studies evaluating pharmacokinetic interactions between CBD and AEDs reported increased serum levels of rufinamide, topiramate, zonisamide, and eslicarbazepine (Devinsky et al., 2018; Gaston et al., 2017).

Elevations in AST and ALT have been reported in individuals taking CBD. In one pediatric cohort (ages 4–10 years), 6 of 34 patients developed transaminase elevations greater than three times the upper limit of normal, without evidence of drug-induced liver injury. The most commonly reported adverse effects included pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia, and abnormal behavior (Devinsky et al., 2018). A systematic review by Skelley et al. encompassing eight studies noted overall minimal adverse effects, although sedation, dry eyes, fatigue, and sexually inappropriate behaviors were reported. Mild sedation observed in one study was noted to improve with continued use. Across a meta-analysis of eight studies, reported adverse effects included drowsiness, headache, nausea, and rash (Han et al., 2024).

Per a systematic review in 2020 by Skelley et al., CBD was identified as a potentially effective alternative therapy in the acute treatment of generalized anxiety disorder, social anxiety disorder, and anxiety related to PTSD. However, there was substantial heterogeneity across studies with respect to dosage, route of administration, product purity, and regulatory oversight, all of which contributed to variability in outcomes. Oral capsule dosing ranged widely, from 6 mg daily to 400 mg per dose. One randomized controlled trial utilizing a 150 mg nanodispersible CBD oral solution demonstrated significant reductions in GAD-7 scores (−7.02) and Hamilton Anxiety Rating Scale (HAM-A) scores (−11.9) (Gundugurti et al., 2024). Han et al. 2024 reported a significant anxiolytic effect of CBD across 316 participants in a meta-analysis, with a large effect size (Hedges' g = −0.92, 95% CI −1.80 to −0.04).

In contrast, a randomized controlled trial examining CBD as an adjunct to exposure therapy in treatment-refractory anxiety disorders failed to demonstrate significant differences compared with placebo (Kwee et al., 2022). Additionally, in another study, individuals receiving high-dose CBD (300 mg) compared with low-dose CBD (50 mg) or placebo showed no significant improvement in worry severity or anxiety symptoms over a two-week period (Gournay et al., 2023). Similarly, individuals with high trait paranoia did not demonstrate improvement following exposure to a virtual reality paradigm designed to elicit anxiety (Hundal et al., 2018).

Compared to isolated CBD, cannabis products as a whole are generally advised against in preadolescent and adolescent populations due to well-established risks, including increased incidence of psychosis, mood disorders, and suicidality (Gobbi et al., 2019). It has also been shown that while THC use often results in negative behavioral and psychological effects, CBD is generally considered well tolerated with respect to anxiety, sedation, positive psychotic symptoms, and intoxication when compared with THC exposure (Skelley et al., 2020). Considerable variability exists in CBD formulation and dosing across commercially available products. In an analysis of 80 unregulated CBD products compared with Epidiolex®, THC was detected in 53 samples, with concentrations ranging from 0.008 mg/mL to 2.071 mg/mL. Of these products, 21 labeled as "THC-free" still contained detectable THC levels ranging from 0.015 mg/mL to 0.656 mg/mL. Epidiolex®, included as a regulated comparator, contained a Δ^9-THC concentration of 0.022 mg/mL (± 0.001) (Johnson et al., 2022). Psychoactive effects of THC can occur with 2-3 mg of THC in sensitive individuals (Hall and Pacula, 2010). However, in consideration of varying amount of product use by consumers, multiple doses may result in impairment, intoxication, and/or a positive urine drug screen (Johnson et. al 2023).

Overall, existing data suggest that CBD may offer benefit in select cases of anxiety, though evidence appears less robust in treatment-resistant populations or acute stress paradigms. Additionally, treatment durations of two weeks may be insufficient to capture therapeutic effects. Potential THC contamination remains a significant concern, underscoring the need for careful product selection and verification, as labeling accuracy may be unreliable. Notably, the *Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* issued by WFSBP and CANMAT Taskforce generally omitted cannabinoids, as well as traditional Chinese medicine formulations, citing these as complex and specialized areas beyond the scope of the taskforce (Sarris et al, 2022).

Chamomile (*Matricaria chamomilla*)

Chamomile is an internationally recognized medicinal herb native to southern and eastern Europe and has been used in traditional herbal remedies for thousands of years, including in ancient Egypt, Greece, and Rome. More than 120 chemical constituents have been identified within chamomile, including sesquiterpenes, flavonoids, coumarins, and polyacetylenes (Singh et al., 2011).

In animal models of anxiety, chamomile has demonstrated pharmacological activity. One or more flavonoid constituents appear to exert anxiolytic effects through modulation of γ-aminobutyric acid (GABA), noradrenaline, dopamine, and serotonin neurotransmission, as well as through effects on HPA axis function (Keefe et al., 2016). Apigenin, a key flavonoid constituent,

along with other chamomile components, has been shown to modulate GABA receptor function via ligand activity at the central benzodiazepine binding site, resulting in reduced GABA-activated chloride currents (Keefe et al., 2016; Savage et al., 2018). These mechanisms are consistent with observed sedative and anxiolytic effects, which were attenuated by co-administration of flumazenil, further supporting benzodiazepine-receptor involvement (Savage et al., 2018). Despite these findings, relatively few clinical trials in humans have been conducted to substantiate chamomile's anxiolytic effects (Keefe et al., 2016).

In 2009, the first randomized, double-blind, placebo-controlled trial of chamomile for the treatment of mild to moderate generalized anxiety disorder was conducted. Participants received chamomile extract capsules (220 mg daily) or placebo for eight weeks. The chamomile group demonstrated a significantly greater reduction in mean total Hamilton Anxiety Rating Scale (HAM-A) scores compared with placebo, suggesting modest anxiolytic efficacy in this population (Amsterdam et al., 2009).

Subsequently, a 2016 open-label study evaluated chamomile in patients with moderate to severe GAD. In this study, 179 participants received up to 1,500 mg daily (with the option to reduce to as low as 500 mg when indicated). After eight weeks, 58.1% of participants met criteria for response, defined as a ≥50% reduction in GAD-7 scores and a final Clinical Global Impression–Severity (CGI-S) score of 1–3 (Keefe et al., 2016). Responders continued chamomile therapy for an additional four weeks before entering a randomized relapse-prevention phase, in which participants were assigned to either continued chamomile or placebo. Of the original 179 participants, 93 met response criteria and entered phase 2. During follow-up, chamomile did not appear to significantly reduce the risk of relapse. Notably however, participants maintained on chamomile continued to exhibit significantly lower anxiety symptoms, as well as reductions in body weight and mean arterial blood pressure compared with placebo (Mao et al., 2016).

A 2024 systematic review identified ten clinical trials examining chamomile for anxiety, with nine of ten demonstrating anxiolytic benefit. Across studies, substantial heterogeneity was observed in dosing (250–2,000 mg), formulation (tea versus capsule), and patient populations, with some trials including individuals with comorbid medical conditions such as cancer or postmenopausal status (Saadatmand et al., 2024). The single negative trial involved cancer patients receiving chamomile tea once daily for two weeks, which did not demonstrate anxiolytic benefit (Ghamchini et al., 2019).

Across clinical studies, a proportion of participants discontinued treatment due to adverse events, although no life-threatening reactions were reported. In the 2009 randomized trial, two of 61 participants in the chamomile group discontinued treatment—one due to abdominal discomfort and one due to an allergic reaction (Amsterdam et al., 2009). Interestingly, a total of 11 adverse events were reported in the chamomile group compared with 22 in the placebo group. In the open-label phase of the 2016 study, the most common adverse effect was drowsiness (7.2%), followed by lingering herbal taste (3.9%), with additional reports of diarrhea, nausea, indigestion, and fatigue (Keefe et al., 2016). During the relapse-prevention phase, adverse events were again more frequent in the placebo group, although chamomile-associated effects included congestion, diarrhea, drowsiness, dry mouth, fatigue, flushing, herbal taste, nausea, taste disturbance, urinary frequency, and "wobbly legs" (Mao et al., 2016).

Data on herb–drug interactions involving chamomile remain limited. One notable case report described a 70-year-old patient stabilized on warfarin therapy who developed a retroperitoneal hematoma, hemoglobin of 8 g/dL, and an INR of 7.9 following concurrent use of chamomile lotion applied 4–5 times daily to both legs and ingestion of 4–5 cups of chamomile tea daily (Segal & Pilote, 2006). In vitro studies have demonstrated that crude chamomile essential oil primarily inhibits CYP1A2, with lesser inhibition of CYP3A4, CYP2C9, and CYP2D6 (Ganzera et al., 2006).

Overall, chamomile may be associated with modest improvements in anxiety-related symptoms; however, the underlying mechanisms of action require further characterization. Heterogeneity in product formulation, dosing, and constituent profiles limits the consistency and generalizability of reported findings. Moreover, evidence regarding clinically relevant drug–drug interactions remains sparse, warranting cautious consideration when chamomile is used concurrently with established pharmacotherapies. According to *the Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* issued by the WFSBP and the CANMAT Taskforce, chamomile flowers are not recommended as either monotherapy or adjunctive treatment for generalized anxiety disorder (Sarris et al, 2022). This recommendation reflects mixed clinical evidence, including favorable findings reported by Amsterdam et al. and no significant differences in relapse rates observed by Mao et al., despite an overall favorable safety profile.

Galphimia glauca (*calderona amarilla)*

Galphimia glauca, also known in Spanish as *calderona amarilla* as well as Corpionchi and Golden Boquet, has a long history of use in Mexican traditional medicine as a sedative or nervous tranquilizer (Herrera-Arellano et al., 2007; Romero-Cerecero et al., 2019). One of its principal active constituents, galphimine B, is a nor-seco-triterpene that has demonstrated anxiolytic properties in preclinical models. Proposed mechanisms include selective inhibition of dopaminergic neurons in the ventral tegmental area, modulation of serotonergic pathways in the dorsal hippocampus, and anxiolytic effects that appear independent of GABAergic signaling. Other galphimines have additionally exhibited spasmolytic activity as well (Herrera-Arellano et al., 2007).

Evidence from three randomized controlled trials suggests potential efficacy of *Galphimia glauca* in the treatment of anxiety-related symptoms when compared with benzodiazepines. These trials employed study-specific standardized extracts, with fixed galphimine B dosing defined independently within each protocol. In two studies, 0.345 mg of galphimine B twice daily and 0.175 mg twice daily, were compared with lorazepam controls (1 mg and 0.5 mg twice daily_ over treatment durations of 4 and 15 weeks, respectively. In both trials, reductions in anxiety severity measured by the Hamilton Anxiety Rating Scale were comparable between *G. glauca* and lorazepam (Herrera-Arellano et al., 2007; Herrera-Arellano et al., 2012). Additionally, a separate study comparing 0.374 mg of galphimine B administered once daily with alprazolam 1 mg daily demonstrated similar anxiolytic outcomes over the course of 10 weeks (Romero-Cerecero et al., 2019).

Despite these outcomes, a subsequent meta-analysis identified concerns regarding risk of bias in the trials using lorazepam as a control, as assessed by the Cochrane Collaboration risk-of-bias assessment tool, underscoring the need for additional well-designed studies (Zhang et al., 2022).

Adverse events associated with *Galphimia glauca* were generally mild and most commonly included sedation, gastrointestinal discomfort, headache, and nausea. Additional reported effects included nervousness, palpitations, orthostatic symptoms, sensations of heaviness, weakness, and dry mouth. Overall, *G. glauca* appeared better tolerated than benzodiazepines across the reviewed studies (Herrera-Arellano et al., 2007; Herrera-Arellano et al., 2012; Romero-Cerecero et al., 2019).

In summary, *Galphimia glauca* may offer modest anxiolytic benefit, with a proposed mechanism of action distinct from benzodiazepines and not primarily mediated through GABAergic pathways . While preliminary evidence suggests comparable efficacy and potentially improved tolerability relative to benzodiazepines, limitations in study quality and concerns regarding bias restrict definitive conclusions. Evidence regarding clinically relevant drug–drug interactions remains limited, warranting cautious consideration when patients present using *Galphimia glauca* preparations. According to the *Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* issued by the WFSBP and the CANMAT Taskforce, *G. glauca* is weakly recommended for monotherapy at doses of 350–700 mg twice daily, using preparations standardized to galphimine B (Sarris et al, 2022).

Kava Kava (*Piper methysticum*)

Kava Kava or Kava (*Piper methysticum*) is an herbal preparation derived from extracts of the plant's root and has been investigated for a range of neuropsychiatric and somatic symptoms. Clinical trials have primarily evaluated its potential efficacy in anxiety-related conditions, including excessive worry, insomnia, headaches, muscle strain, and muscle tension (Smith & Leiras, 2018). Beyond its clinical relevance, kava has a complex legal and regulatory history. Traditionally, it has held substantial social, cultural, and economic importance in Pacific Island nations, where it has been consumed for centuries in ceremonial and social contexts. Over time, however, many countries have implemented regulations governing its production, trade, and sale at both domestic and international levels (Economidis et al., 2025).

Concerns regarding hepatotoxicity emerged following reports of liver injury associated with kava use, prompting bans in several countries, including Germany, the United Kingdom, France, Canada, and Japan. Subsequent re-evaluation of available safety data led both Germany and the United Kingdom to overturn their bans in 2014, concluding that the perceived risk of harm was insufficient or comparable to that associated with other available treatments (Economidis et al., 2025). In the United States, in 2002 the Centers for Disease Control and Prevention published a series of cases describing liver failure associated with kava use and cited concerns raised by the Food and Drug Administration regarding hepatotoxic risk (U.S. Food and Drug Administration [FDA], 2002). These concerns were reiterated by the FDA in 2020, although the agency acknowledged that traditionally prepared aqueous kava beverages may be treated as conventional foods under U.S. federal law (FDA, 2020; Hendrickson, 2025).

Pharmacologically, kava demonstrates anxiolytic and muscle-relaxant properties, largely attributed to a class of compounds known as kavalactones. Its psychotropic effects are thought to arise primarily through modulation of GABA neurotransmission. Proposed mechanisms include

upregulation of GABA-A receptor function, blockade of voltage-gated sodium channels, enhanced ligand binding across GABA-A receptor subtypes, reduced excitatory neurotransmitter release, and inhibition of monoamine oxidase B (Sarris et al., 2020; Savage et al., 2017). The principal active kavalactones include kavain and methysticin, with additional contributions from dihydrokavain, dihydromethysticin, yangonin, flavokawain A, and flavokawain B. Extraction methods substantially influence both kavalactone concentration and composition; alcohol-based extractions (e.g., 95% ethanol) yield significantly higher kavalactone content than traditional aqueous preparations. While these compounds are believed to underlie kava's calming effects, they have also been implicated in kava-associated toxicity. Methysticin has been shown to reduce the viability of human lymphoblastoid cells by approximately 40%, while flavokawain B may induce apoptosis via reactive oxygen species pathways and has been associated with the characteristic dermatologic reactions observed with kava use (Smith & Leiras, 2018).

In vitro studies indicate that kava extracts and select kavalactones inhibit multiple human cytochrome P450 enzymes, with the extent of inhibition strongly influenced by extraction method and kavalactone composition. Organic solvent–based extracts demonstrate more robust inhibition of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 than aqueous preparations, likely due to higher total kavalactone concentrations and altered constituent ratios (Côté et al., 2004). Addition in vitro studies utilizing human microsomes have shown marked inhibition of CYP2C9, CYP2C19, and CYP3A4 as well as significant decreases in CYP1A2, CYP2D6, and CYP4A9/11 (Mathews et al. 2002). In contrast, limited in vivo studies in healthy volunteers have demonstrated mixed and generally modest effects, with some evidence of CYP1A2 or CYP2E1 inhibition but little consistent impact on CYP2C19, CYP2D6, or CYP3A4 activity (Russmann et al., 2005; Gurley et al., 2005).

Notably, populations in the South Pacific who consume kava regularly appear to experience a lower incidence of hepatotoxic effects, raising the possibility of genetic or metabolic protective factors associated with traditional patterns of use. Cytochrome P450 2D6 (CYP2D6) is thought to play a role in kavalactone metabolism (Smith & Leiras, 2018). Reduced-function CYP2D6 alleles occur in approximately 7–9% Caucasian individuals, and is close to 0% among Polynesian populations (Wanwimolruk et al., 1998;Poolsup et al., 2000). Population-level differences may partially account for the disproportionate reporting of hepatotoxicity outside of traditional kava-consuming regions. Collectively, available evidence suggests that kava has a clinically meaningful potential to cause drug–drug interactions via inhibition of CYP enzymes responsible for the metabolism of many commonly prescribed medications.

Although several studies have demonstrated potential short-term anxiolytic benefits of kava, evidence for its efficacy in diagnosed generalized anxiety disorder remains inconsistent. A randomized, double-blind, placebo-controlled trial found kava to be ineffective for the treatment of GAD and reported higher rates of liver function test abnormalities, cognitive impairment, and tremor in the kava group (Sarris, 2020). Furthermore, a systematic review of 11 clinical trials concluded that while kava may confer short-term anxiolytic effects, it should not be considered a long-term treatment, particularly given concerns regarding hepatotoxicity with use beyond eight weeks (Smith & Leiras, 2018).

In summary, kava use is associated with ongoing concerns regarding liver injury risk and clinically relevant cytochrome P450–mediated drug–drug interactions. Variability in extraction methods and kavalactone composition further complicates its safety profile. Evidence supporting its use in generalized anxiety disorder is limited, and prolonged use appears to increase risk without clear additional benefit. Patients should be educated regarding these risks and advised to consider alternative first-line treatments when available. According to the *Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* issued by the WFSBP and the CANMAT Taskforce, kava is not recommended for the treatment of anxiety disorders, despite evidence supporting short-term symptom reduction and the observation that severe liver injury appears to be rare (Sarris et al, 2022).

Lavender (*Lavandula angustifolia*)

Lavender is a flowering plant from the Lamiaceae family, encompassing multiple species with overlapping but variably expressed chemical constituents. Across species, lavender contains more than 100 identified chemical compounds, including terpenes, ketones, and polyphenols present in differing proportions. *Lavandula angustifolia*—one of the most commonly studied species—contains several key constituents, most notably linalyl acetate and linalool. Linalool, in particular, is widely considered the primary component responsible for lavender's anxiolytic effects (Donelli et al., 2019).

Multiple extraction techniques have been employed to obtain lavender essential oil; however, Silexan is produced via steam distillation of *L. angustifolia* Miller flowers to generate a standardized essential oil with defined concentrations of linalool and linalyl acetate. Silexan is registered in Germany as an over-the-counter medicinal product and is commercially available in capsule form. Its production emphasizes controlled cultivation, harvesting, and extraction methods to minimize variability in plant composition and ensure consistent concentrations of active constituents (Kasper et al., 2017;Donelli et al., 2019).

Lavender oil is proposed to exert anxiolytic effects through multiple neurobiological mechanisms. Its primary constituents have been shown to antagonize NMDA receptors and inhibit serotonin transporter (SERT) activity. Lavender oil has also demonstrated reversible inhibition of GABA-induced currents and inhibition of voltage-gated calcium channels in murine synaptosomes, primary hippocampal neurons, and selected cell lines. Additional anxiolytic effects may be mediated through modulation of the 5-HT_1A receptor in specific brain regions (Donelli et al., 2019).

A substantial body of evidence supports the use of lavender for anxiety-related conditions. In a systematic review incorporating 37 randomized controlled trials, quantitative synthesis demonstrated significant reductions in anxiety across multiple validated scales (Donelli et al., 2019). Lavender inhalation has been associated with reductions in systolic blood pressure, and oral administration of Silexan 80 mg/day has shown significant anxiolytic effects when administered for at least six weeks (Yoo & Park, 2023; Woelk & Schläfke, 2010). A separate systematic review of 32 studies examining various lavender formulations suggested that multiple delivery modalities may be effective, while also noting that treatment duration influences clinical response—

supporting Silexan 80 mg/day as a potentially favorable option for longer-term use (Sayed et al., 2020).

In multicenter, double-blind randomized trials in patients with generalized anxiety disorder, Silexan 80 mg/day demonstrated reductions in HAM-A scores comparable to lorazepam 1 mg/day over six weeks and to paroxetine 20 mg/day over ten weeks (Woelk & Schläfke, 2010; Kasper et al., 2014). In the same trial against paroxetine, a higher dose of Silexan (160 mg/day) outperformed the 80 mg/day dose (Kasper et al., 2014).

Regarding pharmacokinetics and drug–drug interactions, in vitro studies using human liver microsomes have shown weak inhibitory activity of lavender oil on CYP3A4 and CYP1A2 (Mondal et al., 2023). A dedicated pharmacokinetic "cocktail" study evaluated 16 healthy volunteers receiving Silexan 160 mg/day or placebo for 11 days. By day 11, linalyl acetate levels continued to be negligible and linalool concentrations had reached steady state. Administration of probe substrates demonstrated no clinically relevant effects on CYP1A2, CYP2C9, CYP2D6, or CYP3A4 activity (Doroshyenko et al., 2012). Additional studies using recombinant human cytochrome P450 enzymes have shown CYP2C19- and CYP2D6-mediated allylic hydroxylation and epoxidation of linalool (Mondal et al., 2023). Overall, Silexan appears to have a low potential for clinically meaningful CYP-mediated drug interactions, though continued study may be valuable.

Silexan is generally well tolerated. Reported adverse effects are typically mild and include gastrointestinal discomfort, eructation, and infrequent allergic skin reactions (Kasper et al., 2014, Kasper et al., 2024). Concerns for weak estrogenic effects leading to prepubertal gynecomastia have been made with lavender oil has been noted as well in 3 boys, which may suggests caution in the pediatric population (Henley et al., 2007).

Given its standardized formulation, demonstrated efficacy comparable to established anxiolytic treatments, favorable tolerability profile, and minimal risk of clinically significant cytochrome P450 interactions, lavender oil – particularly in the form of Silexan – remains a viable treatment option for anxiety disorders. According to the *Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* issued by the WFSBP and the CANMAT Taskforce, lavender is provisionally recommended as monotherapy or as an adjunct for the treatment of generalized anxiety disorder. This recommendation is based on evidence from three randomized controlled trials demonstrating efficacy in generalized anxiety disorder, improvements in somatic symptoms such as insomnia and fatigue, and acceptable safety data. Recommended dosing includes standardized capsules containing 80–160 mg daily, or 500–1,500 mg of dried flower twice daily, with preference given to standardized capsule formulations (Sarris et al, 2022).

Rosemary (*Rosmarinus officinalis*)

Rosemary (*Rosmarinus officinalis*) is an evergreen shrub originating from Asia and the Mediterranean region and belongs to the Lamiaceae family, which also includes lavender. Rosemary contains several potentially active constituents, including α-pinene, 1,8-cineole, camphor, carnosol, carnosic acid, rosmarinic acid, and various flavonoids. While rosemary has been associated with a wide range of traditional and proposed uses, its potential effects on anxiety, depression,

and sedation are thought to be mediated in part through actions on GABAergic receptors, as well as through antioxidant mechanisms (Nematolahi et al., 2018)

At the time of publication, clinical data supporting rosemary's psychiatric applications remain limited, with the exception of several randomized controlled studies conducted in select populations, as described in the following paragraph. In preclinical research, rosemary has been investigated for anxiolytic effects using the Elevated Plus Maze (EPM) in rodent models (Abadi et al., 2016). The EPM consists of two open arms and two enclosed arms intersecting at a central platform; increased time spent in the open arms, which lack protective walls, is interpreted as reduced anxiety-like behavior (Walf & Frye, 2007). A dose-dependent anxiolytic effect was observed, with rosemary administered at 400 mg/kg producing behavioral effects comparable to diazepam 1 mg/kg (Abadi et al., 2016). Additionally, Sasaki et al. (2021) noted this as well as well as reported increased brain oxytocin levels, attenuation of corticosterone responses to stress, and prevention of stress-induced reductions in both serum and brain brain-derived neurotrophic factor.

Regarding human populations, several randomized controlled trials have evaluated rosemary and its constituents, demonstrating potential efficacy across a range of anxiety and mood-related outcomes. In a double-blind RCT of 68 students receiving 500 mg rosemary versus placebo, anxiety improved significantly on the Hospital Anxiety and Depression Scale, along with favorable changes in sleep quality, depression scores, and memory performance (Nematolahi et al., 2018). A separate randomized controlled trial involving 63 participants aged ≥65 years with type 2 diabetes examined aromatherapy with lavender, rosemary, or no intervention on anxiety, cognition, and sleep quality; anxiety outcomes assessed using the State Anxiety Inventory demonstrated reduced scores in the rosemary group compared with control, with effects comparable to lavender (Can et al., 2024). In another study of 236 individuals undergoing general surgery, rosemary aromatherapy was associated with significant reductions in preoperative anxiety and produced greater anxiolytic effects than rosemary combined with music therapy alone (Mank-Halati et al., 2024). The Profile of Mood States, Second Edition (POMS-2), assesses total mood disturbance by summing five negative mood clusters—Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, and Tension-Anxiety—and subtracting the Vigor-Activity score (Heuchert & McNair, n.d.); in a small 4-week study of Japanese men receiving 8 mg rosmarinic acid, favorable findings were reported for Tension-Anxiety, Vigor-Activity, fatigue upon awakening, daytime sleepiness, and psychomotor speed, although the small sample size and potential confounders limited interpretability (Araki et al., 2020). Finally, one trial utilizing the Hospital Anxiety and Depression Scale and the Beck Depression Inventory-II demonstrated significant reductions in both depression and anxiety symptoms compared with placebo after 8 weeks of treatment (Azizi et al., 2022).

In the same study, mild adverse effects of statistical significance were reported, including heartburn and perceived improvements in memory (Azizi et al., 2022). Nematolahi et al. (2018) similarly reported mild side effects in a small number of participants, including a diuretic effect (n = 3), skin improvements (n = 3), increased libido (n = 2), and increased appetite (n = 1). In toxicological studies, rats administered a combination of acetone and supercritical carbon dioxide rosemary extracts at doses of 3,400 mg/kg demonstrated overall tolerability, with the exception of liver enlargement and hepatocellular hypertrophy; these hepatic changes were attributed to

induction of cytochrome P450 enzymes and were reported to be reversible (Phipps et al., 2021). Additionally it has been suggested that very high doses of rosemary may adversely affect spermatogenesis, testosterone levels, sperm density, and motility, with further concerns raised regarding genotoxicity and fetal anomalies at extreme exposures (Rahbardar & Hosseinzadeh, 2025). In another study, the oral median lethal dose of rosemary in rats was reported to exceed 2,000 mg/kg body weight (Anadón, 2008).

With respect to drug–metabolizing enzyme interactions, rosmarinic acid has been shown to inhibit CYP2C19 and CYP2E1, as well as UGT1A1, UGT1A6, and UGT2B7 through competitive mechanisms. Several enzymes appear to be involved in the metabolism of rosmarinic acid itself, including CYP1A2, CYP2C19, CYP2E1, CYP3A4, and UGT1A1, UGT1A6, and UGT2B7. These findings were demonstrated using human recombinant isozyme systems and human liver microsomes. Based on previously reported plasma concentrations, these data suggest that oral administration containing approximately 200 mg of rosmarinic acid may be more likely to inhibit UGT enzymes in humans rather than CYP isoforms (Kim et al. 2019).

At present, rosemary appears to lack sufficient high-quality clinical evidence to support its routine use for anxiety disorders unrelated to comorbid medical conditions or situational stressors. The generalizability of findings from the limited populations studied remains unclear, and over the past two decades there has been a notable absence of meta-analyses or systematic reviews addressing its psychiatric applications. Furthermore, while rosmarinic acid demonstrates enzyme-mediated interactions, other constituents of rosemary may also contribute to its pharmacological activity and warrant further investigation. A lack of standardized dosing further limits clinical applicability. Notably, rosemary is not addressed in the *Clinician Guidelines for the Treatment of Psychiatric Disorders with Nutraceuticals and Phytoceuticals* (Sarris et al, 2022). For these reasons, rosemary most likely requires additional rigorous study and cautious evaluation before it can be recommended for the treatment of anxiety disorders .

Saffron (*Crocus sativus*)

Saffron (*Crocus sativus*) is a traditional plant originating from regions of East Asia and the Middle East and has historically been used for a wide range of medicinal purposes. The saffron flower contains three yellow pistils and three long reddish-orange stigmas, which are dried and manually harvested; these stigmas constitute the primary source of saffron used for medicinal and culinary purposes. Historically, saffron has been used for its purported anticonvulsant, antispasmodic, anxiolytic, antidepressant, and aphrodisiac properties. Chemically, saffron contains more than 150 volatile and non-volatile compounds, with several bioactive constituents thought to underlie its antidepressant and anxiolytic effects. These include carotenoids such as crocin and crocetin, as well as aldehydes including safranal and picrocrocin. Although its precise mechanisms of action require further confirmation, saffron's effects have been hypothesized to involve antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties (Han et al., 2024). Additionally, modulation of monoaminergic neurotransmission has been proposed, with effects on serotonin, dopamine, and norepinephrine pathways. Crocin has been noted to inhibit monoamine oxidase-A and -B and to exhibit NMDA receptor antagonism (Siddiqui et al. 2022).

In a systematic review of 23 studies, saffron demonstrated a large positive effect size compared with placebo for symptoms of depression and anxiety. The authors identified evidence of publication bias using Egger's test, as well as limited regional diversity among included studies. Despite these concerns, correction for publication bias using trim-and-fill methodology resulted in an increased effect size for saffron. The authors concluded that there were insufficient studies to conduct a meta-analysis comparing saffron with antidepressant medications for anxiety outcomes (Marx et al., 2019).

A separate meta-analysis of eight randomized controlled trials compared saffron with SSRIs for depression and anxiety. Of these studies, four included anxiety outcome measures, such as the Hamilton Rating Scale for Anxiety and the Beck Anxiety Inventory. Across these four trials, no statistically significant differences were observed between saffron and SSRIs in reducing anxiety symptoms. Notably, all eight studies demonstrated no significant differences between treatments for depressive symptoms. Comparators included: saffron 15 mg twice daily versus fluoxetine 20 mg twice daily over six weeks in individuals with irritable bowel syndrome; saffron 15 mg daily versus sertraline 50 mg daily in women with postpartum depression; saffron 15 mg daily versus fluoxetine 20 mg daily in adults aged 18–60 with obsessive-compulsive disorder; and saffron 30 mg daily versus citalopram 40 mg daily in individuals with depression and anxious distress. Across studies, fewer adverse events were reported in participants receiving saffron; however, the overall quality of this evidence was rated as low (Shafiee et al.).

Another meta-analysis encompassing 46 studies found saffron to be non-inferior to standardized pharmacologic treatments for affective disorders. Significant heterogeneity was identified, and to minimize false-positive findings, analyses adjusted for a limited number of covariates, including study duration and daily saffron dose. Subgroup analyses demonstrated significantly greater improvements in anxiety symptoms among participants aged ≥40 years, those receiving treatment for longer than eight weeks, and when anxiety was assessed using the Beck Anxiety Inventory (Han et al. 2024). Beyond anxiety, saffron stigmas have been evaluated in more than 20 randomized clinical trials for major depressive disorder. While many of these studies were limited by small sample sizes and short durations (typically 4–8 weeks), they generally demonstrated greater antidepressant effects than placebo and comparable efficacy to conventional antidepressant medications (Lopresti et al. 2025).

Affron® is a standardized saffron extract manufactured using high-performance liquid chromatography (HPLC) and standardized to contain >3.5% lepticrosalides, a measure of bioactive saffron compounds including safranal and crocin isomerssa. In recent years, several randomized controlled trials have evaluated its clinical utility. In a study of adolescents, 80 participants aged 12–16 years with mild to moderate anxiety or depressive symptoms demonstrated improvements in overall internalizing symptoms, including separation anxiety, social phobia, and depression, after receiving 14 mg of Affron® daily compared with placebo, as measured by the Revised Child Anxiety and Depression Scale youth self-report (Lopresti et al., 2018). In a four-week study of 128 adults, reductions in negative mood and anxiety-related symptoms were observed at a dose of 28 mg/day, whereas no significant treatment effect was seen at 22 mg/day, suggesting a dose-dependent response (Kell et al., 2017). More recently, a two-arm, 12-week trial involving 218 adults aged 18–70 with subclinical depression demonstrated greater improvements in depression, anxiety, and stress among participants receiving saffron 14 mg twice daily compared

with placebo. At week 12, reductions in depressive symptoms were 53% in the saffron group versus 39% in the placebo group, as measured by the DASS-21 depression subscale. After controlling for baseline differences, anxiety—assessed as a secondary outcome using the DASS-21 anxiety subscale—did not differ significantly between groups (Lopresti et al., 2025).

While most studies have shown saffron to be generally well tolerated, with adverse event rates comparable to placebo and conventional pharmacologic treatments, reported side effects have been documented. A review of multiple studies identified adverse effects including dry mouth, headache, gastrointestinal symptoms, dizziness, fatigue, drowsiness, and changes in appetite. In some cases, worsening anxiety symptoms or induction of hypomanic symptoms have also been reported, highlighting the need for cautious use in susceptible individuals (Bostan., 2017). In addition to these symptoms saffron has shown inhibitory effects at CYP1A1/2, CYP2E1, as well as CYP3A4 (Bathai et al., 2025)

Overall, saffron demonstrates some evidence for reducing anxiety symptoms, with several studies suggesting efficacy comparable to first-line pharmacologic agents. The presence of multiple bioactive constituents and the availability of standardized extracts such as Affron® may enhance consistency across preparations. However, while evidence supporting antidepressant effects appears relatively robust, findings related to anxiety outcomes are less consistent. Additionally, saffron is associated with cytochrome P450 interactions, and given the mixed evidence for anxiety-specific efficacy, careful consideration of alternative treatments may be warranted. In accordance with the WFSBP and CANMAT guidelines, saffron is provisionally recommended as monotherapy for mild to moderate depression at doses of approximately 30 mg daily, though its role in the treatment of anxiety disorders remains largely unaddressed (Sarris et al, 2022).

St. John's Wort (*Hypericum perforatum* L.)

Extracts of *Hypericum perforatum* L., commonly known as St. John's wort (SJW), have been used in folk medicine for centuries. In Germany, licensed extracts have been utilized for a broad range of indications, including anxiety, depressive disorders, and sleep disturbances (Linde et al., 2008) While the antidepressant evidence for SJW will be briefly reviewed for completeness, the primary focus of this section is its evidence base in anxiety-related conditions as relevant to the present review.

SJW contains multiple bioactive constituents thought to contribute to its pharmacological effects. At least seven major groups of compounds have been identified, including naphthodianthrones (e.g., hypericins), flavonoids (e.g., quercetin), biflavonoids (e.g., biapigenin), xanthones, and phloroglucinol derivatives (e.g., hyperforin). Hypericum extracts have demonstrated antidepressant activity, with whole-plant extracts appearing more consistently effective than isolated constituents (Linde et al., 2008). Mechanistically, St. John's wort is thought to exert serotonergic, dopaminergic, and GABAergic effects. While its binding to GABA receptors has been thought to explain its role in OCD and anxiety - it has also been propose that its binding of GABA receptors may also decrease binding to GABA, potentially lowering CNS depression (Kobak et al., 2005).

A Cochrane review evaluated multiple double-blind, randomized trials in which SJW monotherapy was compared with placebo or synthetic antidepressants over a four-week period. This

review analyzed 37 trials involving 4,925 patients. Overall, SJW was associated with greater improvement in symptoms of mild-to-moderate depression compared with placebo and demonstrated comparable efficacy to synthetic antidepressants. However, a pooled analysis of six more recent, larger, and methodologically rigorous trials limited to patients with major depressive disorder showed minimal benefit compared with placebo. The review also noted that SJW was associated with fewer adverse events than older antidepressants and slightly fewer adverse effects than selective serotonin reuptake inhibitors (SSRIs). Important limitations highlighted included concerns regarding study heterogeneity, potential bias, and variability in pharmaceutical quality (Kobak et al., 2005).

Despite these concerns, additional support for the antidepressant efficacy of SJW exists. Current WFSBP and CANMAT Taskforce guidelines recommend its use as monotherapy for mild-to-moderate depression, with dosing of flower extracts ranging from 600 to 1,800 mg per day (3:1–7:1 extract depending on product), standardized to approximately 0.2–0.3% hypericin and/or 5–6% hyperforin, administered once to three times daily depending on formulation. These guidelines cite one randomized controlled trial demonstrating superiority of SJW compared with paroxetine, as well as meta-analytic evidence supporting its efficacy in major depressive disorder. Nevertheless, similar concerns regarding extract standardization and product quality are acknowledged (Sarris et. al, 2021).

In contrast, evidence specifically evaluating St. John's wort for anxiety disorders appears limited. While it has historically been used for anxiety and to "calm the mind," these effects may largely reflect improvements in comorbid depressive symptoms. A systematic review of 24 studies examining eight complementary and alternative medicines (CAMs) included six studies involving 762 patients that evaluated St. John's wort. This review concluded that the evidence was largely insufficient to support its use as an effective anxiolytic, although three studies reported positive findings. Interpretation was limited by frequent use of combination therapies and an overall lack of consistent positive evidence (Lakhan and Vieira; 2010). Additionally, a review of 10 clinical practice guidelines identified two guidelines that addressed SJW, both generally recommending against its use in social anxiety disorder (Zhao et al., 2023). Katzman et al. (2014) noted a possible role for SJW in obsessive–compulsive disorder; however, this observation was again limited by poor product standardization and substantial variability. Notably, a 12-week double-blind study involving 60 individuals failed to demonstrate efficacy.

SJW has also been identified as a significant risk for drug–drug interactions. Most prominently, it induces CYP3A4, CYP2E1, CYP2C19, and P-glycoprotein (P-gp). As a result, it may interact with numerous medications, including anticonvulsants, oral contraceptives, antiretroviral therapies, antineoplastic agents, digoxin, warfarin, and cyclosporine. Additionally, SJW has been shown to reduce benzodiazepine levels in healthy individuals (Borelli and Izzo, 2009; Hammerness et al., 2003). Other reported adverse effects include exacerbation of psychotic symptoms in individuals with schizophrenia or bipolar disorder, induction of manic symptoms, tachycardia, hallucinations, hypertension, diarrhea, agitation, increased body temperature, and photosensitivity (Peterson and Nguyen; 2023). Despite these risks, some evidence suggests it may be better tolerated than older antidepressants and associated with slightly fewer adverse effects than SSRIs (Linde et al; 2008)

Overall, the evidence supporting SJW for anxiety disorders remains limited and inconsistent. While some data support it's use in mild-to-moderate depression—a condition frequently comorbid with anxiety—concerns regarding lack of formulation standardization, clinically significant drug interactions, and mixed efficacy findings warrant caution. These factors underscore the importance of counseling patients that "natural" remedies may still exert meaningful pharmacological effects. At present, available evidence does not consistently support SJW as an effective intervention for primary anxiety disorders.

Passionflower (*Passiflora incarnate*)

Passionflower (*Passiflora incarnata* L.) is a perennial fruit-bearing plant native to South America, Australia, and Southeast Asia. Multiple parts of the plant, including the flowers and fruits, have been used medicinally for a variety of indications, most notably for anxiolytic effects, as well as for the treatment of burns, diarrhea, painful menstruation, hemorrhoids, morphine dependence, and insomnia. The primary phytochemicals identified in *Passiflora incarnata* include flavonoids (apigenin, luteolin, quercetin, and kaempferol) and flavonoid glycosides (vitexin, isovitexin, orientin, and isoorientin) (Janda et al., 2020).

The precise mechanism of action remains under investigation. Some studies suggest modulation of the gamma-aminobutyric acid (GABA) system, although one study proposed antagonism at the GABA-B receptor, with minimal effect on the GABA-A receptor. Additional proposed mechanisms include involvement of opioid pathways and oleamide-based cannabimimetic activity (Janda et al., 2020).

A systematic review examining nine studies reported reductions in anxiety levels following administration of passionflower preparations, though effects were less pronounced in individuals with mild symptoms. Study designs varied substantially with respect to duration (ranging from single-day preoperative use to 30-day courses), indication, and primary outcomes. Several studies focused on preoperative anxiety, while others assessed sleep, cognitive function, or comparative efficacy against agents such as oxazepam, midazolam, and melatonin (Janda et al. 2020). In a study comparing *Passiflora incarnata* 260 mg with midazolam 15 mg administered orally 30 minutes prior to mandibular third molar extraction, no significant differences were observed in blood pressure, heart rate, or oxygen saturation. Over 70% of participants in both groups reported feeling either somewhat calm or mildly anxious. While overall anxiolytic effects were similar, approximately 20% of individuals in the midazolam group reported amnesia (Dantas et al., 2017). Similarly, a double-blind, placebo-controlled trial demonstrated that administration of *Passiflora* 500 mg 120 minutes prior to ambulatory surgery produced anxiolytic effects comparable to oxazepam 10 mg (Azimaraghi et al., 2017). Other additional studies assessing passionflower for preoperative anxiety, particularly in tooth extraction, have demonstrated significant benefit compared with placebo and non-inferiority to pharmaceutical comparators as well (Valasquez et al., 2024; Aslanargun et al., 2012, Soares da Cunha et al., 2021; Christoffoli et al 2021).

Outside of randomized trial evaluating preoperative anxiety, one study did evaluate treatment of GAD per DSM-IV criteria, 18 participants received passionflower (45 drops/day plus placebo) and 18 received oxazepam 30 mg/day over a four-week period. Although oxazepam

demonstrated a more rapid onset of action, it was associated with significantly greater impairment in job performance. Overall results suggested that passionflower was comparably effective in managing GAD, though the authors emphasized the need for larger-scale trials (Akhonsazadeh et al., 2002). A Cochrane review identified one study showing no difference in efficacy between benzodiazepines and passionflower. Additionally this review brought forth another favoring passionflower, and one demonstrating lower rates of drowsiness compared with mexazolam, though neither reached statistical significance. The authors concluded that the available evidence was insufficient to draw definitive conclusions regarding the efficacy of passionflower for anxiety (Miyasaka et al. 2007).

Overall, passionflower appears to be better tolerated than many pharmaceutical comparators. Reported adverse effects include at the propensity for at least mild symptoms of somnolence, drowsiness, dizziness, confusion, ataxia, allergic reactions, and impaired job performance in a few individuals, as noted in a study by Akhonsazadeh et al. (2002). In the study by Dantas et al. (2017), somnolence was reported by 82.5% of individuals receiving midazolam compared with 50% of those receiving passionflower. Additionally, pharmacological profiles of certain extracts suggest that high doses may result in central nervous system depression, bradycardia, prolonged QTc, and ventricular tachycardia (Miyasaka et al. 2007).

At present, there is limited data regarding potential drug–drug interactions involving *Passiflora incarnata*, and well-characterized cytochrome P450 interactions have not been clearly established. However, it has been reported to potentiate the effects of pentobarbital, enhance the sedative effects of benzodiazepines, and increase the potency of St. John's wort (Speroni et al 1996; Miyasaka et al. 2007; Fiebich et. al., 2011) . The clinical significance of these interactions remains unclear.

While several randomized controlled trials support the use of passionflower for preoperative anxiety, data regarding its efficacy in DSM-5–defined anxiety disorders remain limited. Passionflower may represent a promising agent for further investigation; however, additional high-quality studies are needed to better characterize its therapeutic efficacy, safety profile, potential drug interactions, standardization, and optimal dosing strategies.

Discussion

Several reviews have examined herbal and plant-derived agents used in the treatment of anxiety, including anxiety occurring alongside medical and psychiatric comorbidities (Yeung et al., 2018; Chen et al., 2022; Lakhan & Vieira, 2010; Zhang et al., 2022; Sarris, 2011; Sarris, 2018). Despite this body of literature, formal clinical guidelines remain somewhat limited. The WFSBP and CANMAT guidelines act to primarily summarize existing studies and provide guidance as to whether the evidence may support utilization. The aim of this narrative review was to further examine the clinical utility of commonly referenced plant-derived supplements while simultaneously exploring the potential risks and drug interactions of these agents to assist clinicians in making informed, collaborative treatment decisions with patients.

Among the reviewed agents, lavender (particularly standardized Silexan preparations) and ashwagandha currently possess the strongest evidence base. Both agents have demonstrated

clinically meaningful reductions in anxiety symptoms across multiple randomized controlled trials and systematic reviews, exhibit favorable tolerability profiles, and have received provisional recommendations from the WFSBP and CANMAT Taskforce (Sarris et al., 2022; Donelli et al., 2019; Kasper et al., 2014; Woelk & Schläfke, 2010; Arumugam et al., 2024; Marchi et al., 2025). Furthermore, both appear to have relatively limited potential for clinically significant cytochrome P450-mediated drug interactions when compared with several alternative herbal products (Doroshyenko et al., 2012; Raichura et al., 2025).

Several additional agents demonstrated promising but less definitive evidence. Saffron, cannabidiol, passionflower, and *Galphimia glauca* have each shown anxiolytic benefits in selected studies, though limitations including small sample sizes, inconsistent formulations, lack of standardization, and limited replication reduce confidence in their routine clinical application (Han et al., 2024; Marx et al., 2019; Skelley et al., 2020; Gundugurti et al., 2024; Janda et al., 2020; Akhondzadeh et al., 2002; Herrera-Arellano et al., 2007; Romero-Cerecero et al., 2019). These agents may warrant consideration in select patients, particularly when conventional treatments are poorly tolerated or when patients express strong interest in complementary approaches. However, clinicians should carefully review potential adverse effects, product quality concerns, and possible drug interactions before recommending their use.

Chamomile and rosemary demonstrated more modest and inconsistent evidence. While both agents have shown potential anxiolytic effects in selected populations, the available literature remains limited by heterogeneity in dosing, formulation, study design, and outcome measures (Saadatmand et al., 2024; Amsterdam et al., 2009; Keefe et al., 2016; Nematolahi et al., 2018; Can et al., 2024). At present, the evidence supporting their use appears insufficient to support routine recommendation for anxiety disorders.

Conversely, kava and St. John's wort present more significant concerns. Although kava has demonstrated short-term anxiolytic efficacy in some studies, persistent concerns regarding hepatotoxicity and cytochrome P450-mediated drug interactions substantially limit its clinical utility (Smith & Leiras, 2018; Sarris et al., 2020; Economidis et al., 2025). Similarly, St. John's wort possesses extensive interaction potential through induction of CYP3A4, CYP2C19, and P-glycoprotein pathways, which may alter concentrations of numerous commonly prescribed medications (Borrelli & Izzo, 2009; Hammerness et al., 2003). Furthermore, evidence supporting its use in primary anxiety disorders remains inconsistent despite stronger evidence for depressive disorders (Lakhan & Vieira, 2010; Zhao et al., 2023; Linde et al., 2008).

The use of herbal remedies introduces several variables that often result in heterogeneous findings across studies. Many botanicals contain multiple active compounds, and their composition may vary substantially depending on extraction methods and preparation processes. Lavender, particularly the standardized preparation Silexan, represents an example in which efforts to isolate, purify, and standardize active constituents have improved study consistency and demonstrated clinical benefit. Such approaches may also facilitate greater comparability across future studies. Mixed herbal formulations were not included in this review due to the difficulty of attributing effects to individual components; however, it should be acknowledged that even single botanical agents often contain numerous biologically active compounds, creating complex interactions that may contribute to therapeutic effects. Additionally many studies conducted were

limited to select populations or short time frames. Larger studies and time frames in conjunction with standardized extracts may potentially offer further clarity in the future.

Anxiety itself may also be considered a heterogeneous construct. Although the initial search strategy attempted to focus specifically on anxiety outcomes, symptom presentation varies widely among individuals. Anxiety may be influenced or exacerbated by life stressors, changes in physical health, and comorbid psychiatric conditions. Additionally, several agents excluded from this review primarily measured cognitive outcomes; however, cognition and anxiety are closely intertwined, as cognitive dysfunction may both contribute to anxiety and be affected by it as well.

As previously mentioned, blueberries were excluded from this review due to the limited available literature. Nevertheless, their exclusion highlights a broader point regarding the potential influence of diet and commonly consumed substances on mood. Whether classified as foods, herbs, or pharmacologic agents, many compounds we consume may exert biologically meaningful effects. Although this review focused on "phytoceuticals," the boundaries of this term remain somewhat ambiguous. For example, L-theanine was excluded because it is typically categorized as an amino acid supplement rather than a plant-derived compound, yet plants and teas may naturally contain L-theanine and similar molecules (Williams et al., 2020). This further illustrates the complexity involved in defining and studying the wide range of biologically active substances humans consume on a daily basis.

Finally, although many patients seek herbal remedies and may conduct their own research prior to clinical encounters, it remains essential for clinicians to understand both the potential benefits and the associated risks of these therapies. Expanding clinician knowledge in this area can help guide safe, evidence-informed discussions with patients, potentially improving outcomes while reducing harm. Continued investigation into herbal and plant-derived compounds may contribute not only to the development of novel treatments but also to a deeper understanding of the biological mechanisms underlying mood and anxiety disorders, while strengthening the collaborative physician–patient relationship.

Conclusion

Among the herbal supplements in this paper, ashwagandha and lavender (particularly the standardized preparation Silexan), demonstrate the most consistent evidence and may be considered among the more strongly supported botanical options for anxiety. Galphimia glauca has also shown potential benefit in several studies, though the evidence remains limited. Other agents – including CBD, and saffron – have demonstrated signals of possible benefit; however, the current literature remains mixed, with studies suggesting both positive effects and inconsistent findings. In these cases variability in preparations highlights the importance of standardized dosing and extraction methods in future research. Saffron may be particularly beneficial in individuals with comorbid depression and anxious distress, as several studies suggest improvements in both mood and anxiety-related symptoms.

Conversely, some herbal therapies carry important limitations. Some appear to require further studies to support their use including rosemary and chamomile. Others appear limited to studies

in select populations, such as the use of passionflower in preoperative anxiety, particularly in studies involving anxiety prior to tooth extraction, though further research is needed to determine whether these effects generalize to broader anxiety disorders. St. John's wort has limited evidence supporting its use for anxiety specifically and is associated with significant drug–drug interactions, which may restrict its clinical utility. Kava has demonstrated short-term anxiolytic effects in several studies; however, its use has been associated with potential hepatotoxicity and reports of liver injury, raising significant safety concerns. While it may provide short-term symptom relief, it does not appear to be an appropriate agent for long-term treatment, and given the overall risk–benefit profile, it does not appear currently appear to be recommended for the treatment of anxiety.

When patients inquire about herbal or complementary treatments, clinicians should discuss both the potential benefits and associated risks, including possible drug–herb interactions with existing pharmacotherapies. Familiarity with standardized extracts, appropriate dosing, and the current evidence base may help clinicians guide patients toward safer and more informed use of these therapies while minimizing the risk of adverse effects or inappropriate dosing.

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Case Report

Probable Behavioral Variant Frontotemporal Dementia in a 33-Year-Old: A Case Report and Review of Early-Onset Presentations

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CONFLICTS OF INTEREST STATEMENT

Dr. Glenn reported the following disclosures: speaker for Alkermes and Advisory Board for Bristol Myers Squibb. Dr. McMahon does not have any conflicts of interest to report regarding this case report.

ABSTRACT

Background: Frontotemporal dementia (FTD) is a clinical term for a group of neurodegenerative disorders with prominent behavioral changes, loss of executive control, aphasia, and motor symptoms. FTD is a known cause of dementia in patients under the age of 65. More rarely, the disease can occur in patients under the age of 45. The disease can be familial or sporadic. While some genetic mutations are known to be associated with FTD, further research into the genetic causes of this disease is ongoing. Diagnosis can be challenging given the lack of laboratory testing and symptom overlap with psychiatric illness and other neurological conditions. This often leads to delays in diagnosis.

Case Summary: In this article, we present a case of a 33-year-old male with an unusually early presentation of probable behavioral variant frontotemporal dementia (bvFTD). The patient was initially admitted to an inpatient psychiatric hospital for altered mental status and bizarre behaviors. He presented with odd behaviors such as pulling his car over and walking into traffic, delusions, perseveration, and disorientation. Given his age and symptoms, he was treated for catatonia, psychosis, and obsessive-compulsive disorder with no improvement in symptoms of disinhibition, blunted affect, bizarre behaviors, and limited speech. Due to unclear etiology of symptoms, an MRI of his head was ordered to evaluate possible neurological causes. Head imaging revealed bilateral atrophy in the frontal and temporal regions of the brain, consistent with probable frontotemporal dementia. Genetic testing did not show any known genetic causes for FTD. Given the MRI results and the patient's clinical syndrome, the patient meets criteria for a diagnosis of probable bvFTD using the International Consensus Criteria for Behavioral Variant FTD (FTDC).

Outcome: Following MRI findings, antipsychotics were discontinued, and benzodiazepines were tapered to discontinuation. The patient continued citalopram for anxiety and started methylphenidate for impulse control. Genetic testing was completed on the patient, and no pathogenic genetic mutations that are associated with genetic causes of neurodegenerative diseases like FTD were detected. However, an OPTN variant of uncertain significance was detected, which merits further investigation. His life partners obtained guardianship with the goal of the patient remaining in the home safely as long as possible. The patient continues to be followed by outpatient neurology, psychiatry, palliative care, and internal medicine. The patient continues to demonstrate progressive deterioration in language and executive functioning, consistent with the expected neurodegenerative course of behavioral variant frontotemporal dementia.

Conclusions: Frontotemporal dementia is a known cause of dementia in patients under the age of 65. It is uncommon for patients to present before the age of 45. However, in young patients with progressive disinhibition, personality changes, and treatment resistance, neuroimaging should be considered, particularly when accompanied by rapid functional decline.

Keywords: Frontotemporal dementia, behavioral variant, early onset, mental health

Introduction

Frontotemporal dementia (FTD) is a clinical term used for a diverse group of syndromes with prominent behavioral changes, loss of executive function, aphasia, and motor symptoms. The term frontotemporal lobar degeneration (FTLD) is often used to describe the various neurodegenerative pathologies that lead to the degeneration of the frontal and temporal lobes, which are responsible for FTD. There are three primary subtypes of FTD: behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent agrammatic variant primary progressive aphasia (nfvPPA). Other related FTD-spectrum disorders include frontotemporal dementia with motor neuron disease (FTD-MND), progressive supranuclear palsy syndrome (PSP-S), and corticobasal syndrome (CBS).[1] The subtype of FTD called behavioral-variant frontotemporal dementia (bvFTD) includes symptoms such as apathy/inertia, loss of empathy/sympathy, disinhibition, hyperorality, perseverative or compulsive behaviors, and a dysexecutive neuropsychological profile.[2]

FTD is a common cause of dementia, with one study finding a pooled crude incidence of 2.28 per 100,000 person-years and a pooled prevalence of 9.17 per 100,000 people.[3] In the same study, bvFTD was found to have a pooled crude incidence of 1.20 per 100,000 person-years and a prevalence of 9.74 per 100,000 people.[3] Further, this study suggested that FTD rates increase with age and peak in the seventh decade of life.[3] The majority of FTD cases occur between 45 and 64 years of age.[4] One study found the median age of onset for patients with FTD is 58 years old.[5] There is also some evidence that bvFTD may occur more frequently in men, while primary progressive aphasia may occur more frequently in women.[6] FTD is also a recognized cause of early-onset dementia, meaning the development of dementia before the age of 65, with one study finding a global prevalence of 2.3 per 100,000 population worldwide in patients aged 30 to 64.[7] This study found the peak prevalence of FTD is between ages 55 and 59 for patients aged 30 to 64.[7]

Very early onset FTLD (VEO-FTLD) is a subset of FTLD where patients present with symptoms before 45 years of age. VEO-FTLD most commonly presents as the bvFTD clinical subtype and frequently includes symptoms of disinhibition, apathy, cognitive deficits, and Parkinsonism.[8] Some researchers feel VEO-FTLD may have unique genetic, neuropathological, and clinical characteristics.[8]Evidence regarding the prevalence of VEO-FTLD remains limited, though one study estimated that approximately 10% of FTLD cognitive syndromes occur before 45 years of age.[4]

FTD can occur sporadically or be inherited genetically.[9] In one study, some family history of an FTLD-spectrum disorder was found in 41.8% of patients who had an FTLD-spectrum disorder and 58% of patients with bvFTD.[10] In the same study, 10.2% of patients with an FTLD-spectrum disorder were found to have a clear autosomal dominant history of an FTLD-spectrum disorder, compared to 20% of patients with bvFTD.[10] Multiple genes have been associated with the development of FTD. Autosomal dominant mutations in three genes are the most common: chromosome 9 open reading frame (C9orF72), Progranulin (GRN), Microtublin-associated protein tau (MAPT).[9] Various less common other genes have also been associated with autosomal dominant FTD.[9]

Diagnosing FTD can be particularly challenging. FTD symptoms often mimic psychiatric conditions like major depressive disorder, OCD, mania, and schizophrenia.[11] It can also mimic other neurological conditions like Alzheimer's disease.[12, 13] One study noted consensus criteria had a high rate of specificity for FTD (100%) but a low rate of sensitivity (36.5%).[14] The sensitivity was higher in this study for MRIs (63.5%) and SPECT/PET Scans (90.5%).[14] FTD misdiagnosis rates are high particluarly in patients with past psychiatric history.[15] It also noted that false positives were often due to errors in reading neuroimaging and neuropsychological testing.[15] Another study noted that over 50% of patients with bvFTD were given a prior psychiatric diagnosis.[16] These challenges make understanding and considering FTD particularly important.

Evaluating a patient who presents with symptoms concerning for FTD requires careful consideration of multiple factors, including clinical interview, collateral information, laboratory findings, imaging, and diagnostic criteria. Changes in cognition, behavior, and language should be thoroughly assessed through interview and collateral information. Laboratory assessment should be conducted to look for other potential causes of changes in cognition and behavior, along with neuroimaging.[17] Genetic testing to assess for known genetic causes of FTD is recommended.[2] Lastly, criteria such as the International Consensus Criteria for Behavioral Variant FTD (FTDC) can be utilized to determine the likelihood that the patient has FTD.[2]

Case Report

A 33-year-old male presented to the emergency room with a chief complaint of walking into traffic after running out of gas. The patient reported feeling "down" but denied this being a suicide attempt. Reportedly, he had been forgetting to eat recently. In the ER, he was noted to be tapping his food with his fingers and mumbling frequently before eating, which he said was him praying. If he could not do it, he said it would kill him. He was also noted to be clapping and stated that if he did not do this, he would urinate. His complete metabolic profile on the day of presentation was unremarkable, with only a mildly elevated alkaline phosphatase level (117). Complete blood count showed an increased white blood cell count (12.0), absolute neutrophil count (8.20), and hemoglobin (16.8). A urine drug screen was only positive for amphetamines. Thyroid-stimulating hormone was within normal limits, and urinalysis was unremarkable.

The patient had a medical history of recent urinary incontinence. He also had a history of a severe bacterial infection during the COVID-19 pandemic, and shortly after, developed a COVID-19 infection that led to him being coded and needing resuscitation. Past psychiatric history appears to have been benign before the COVID-19 pandemic, with his partners describing him as a "normal everyday person". His partners noted he started having depression shortly after these infections. His past psychiatric diagnoses on admission included obsessive-compulsive disorder, attention deficit hyperactivity disorder, and severe anxiety. His partners noted that he started having increased depression, anxiety, and cognitive struggles during the COVID-19 pandemic. He was diagnosed with ADHD by his primary care physician after these cognitive struggles and was treated with stimulants. The patient had one reported suicide attempt during the COVID-19 pandemic two years before admission. He reportedly made this suicide attempt while at work, and his employment was subsequently terminated. He also reportedly made inappropriate comments to coworkers prior to this attempt. Further, he was noted to be delusionally speaking to God after this attempt. He started having increased focus on religion and developed excessive

prayer rituals. There was also an unclear report about him talking about demons flying and beliefs he could communicate to his Jeep through his keys. In general, he was noted to have increased paranoia, perseveration, and distractibility.

Further history gathering showed that the patient started having obsessive-compulsive-like symptoms around late 2023, worsening in the past year before presentation. Most recently, partners noted he had also developed tics and other motor symptoms. He had a history of cannabis use, but he had not used it in 5-7 years. Per the patient's partners, who provided collateral, the patient had also experienced cognitive changes over the past year. He had started displaying memory loss and false memories. He noted that he had been molested. He also noted that he previously had breasts, but they were removed. His partners verified with the patient's parents that this was not the case. They further noted some non-specific irrational behavior starting around 2 weeks before this event. He developed an obsession with feces and putting his finger in his anus. He had been forgetting to eat for around 2 weeks before admission. During this time, he was also in a minor motor vehicle collision. At some point after this, the patient reportedly attempted to walk 8 miles to a gym, partially on or across the highway. Further, he had developed incontinence and bedwetting and was seen for this around 2 weeks before admission. Notably, he had tried to work again but was unemployed at the time of admission due to the workplace being unable to accommodate his frequent urination and associated anxiety. Per a note from November 2024, the patient had been urinating 7-8 times per hour and having nocturia 5-6 times per night. He was treated with fluoxetine and lisdexamfetamine before admission. He was also receiving treatment with IV ketamine and transcranial magnetic stimulation.

Notably, the patient had a family history of bipolar disorder in his sister. He also has an identical twin brother who reportedly had unspecified personality changes after bariatric surgery, which caused strain on their relationship. He did not have any current substance abuse when he presented to the emergency room. As previously noted, his urine drug screen before admission was positive only for amphetamines. This was likely secondary to lisdexamfetamine. The patient was admitted from the emergency room to the acute inpatient psychiatric facility.

The differential diagnoses consisted of catatonia, stimulant-induced psychotic disorder, a thought disorder like schizophrenia or bipolar disorder, obsessive-compulsive disorder, and psychosis due to another medical condition. While on the inpatient unit, the patient displayed many notable behaviors. He often displayed repetitive behaviors, including hitting himself on the top of his head, covering his face, biting the top of his hands, putting his hands in his pants, hitting himself on the thighs, rubbing his stomach, and making hand gestures that consisted of waving and forcefully clapping. He was observed going to the bathroom frequently and displaying repetitive behaviors, including sticking the roll of toilet paper between his legs and against his penis, rocking, and sticking his hands behind his buttocks. He was seen lying in bed, waving his arms and kicking his legs while making a high-pitched wailing sound. He was noted to have attempted to tear his pillow with his teeth in the bathroom. He would climb on top of tables and punch walls. He would frequently try to play in the bathroom and toilet. He defecated in the sink and the shower, and at one point, his bathroom was clogged to the point of needing to be mechanically repaired. He was generally redirectable but minimally interactive with staff. When he was in the ward milieu, he was noted to get too close to other patients. He attempted to elope, including

trying to climb through the ceiling tiles. He would also attempt to open doors, including those of other patient rooms. These behaviors required frequent administration of as-needed medications.

Multiple approaches were attempted to treat him. His Busch Francis score shortly after admission was 10 on 3/9/2025. He was given 2 mg of lorazepam, and 45 minutes later felt drowsy with minimal change in mental status. A repeat Busch Francis on 3/17/2025 scored at 16. Attempts were made to treat this with multiple different doses of lorazepam as well as by augmenting with valproic acid, with little success. Attempts were also made to treat him with risperidone, fluoxetine, clonidine, aripiprazole, and zolpidem, which were all eventually discontinued.

Initial efforts at diagnostic clarity were difficult due to the patient showing little response to treatment. His lack of response to lorazepam made a diagnosis of catatonia less likely. Further, his lack of response to treatment using antipsychotics and a mood stabilizer made a diagnosis of bipolar disorder or schizophrenia less likely. Further, a diagnosis of obsessive-compulsive disorder appeared less likely given the profound nature of his behavioral disturbances and disorganization. Given the patient's UDS being positive for amphetamines and his having a prescription for lisdexamfetamine outpatient, stimulant-induced psychosis was an initial consideration. However, lisdexamfetamine was held during admission, and if amphetamines were responsible for his symptoms, they would likely have improved rapidly during his admission. This was not observed, making this diagnosis less likely. Formal psychological testing was considered in this patient but was not completed.

Further laboratory testing was conducted during admission for medical causes of his presentation. NMDA receptor IgG was negative. Syphilis antibody was non-reactive. Quantiferon testing was negative. Serum folate, vitamin B1, and vitamin B12 were within normal limits. Repeat CBC showed resolution of early findings and was unremarkable. Repeat CMP continued to be unremarkable. HIV testing was non-reactive. Vitamin D was low at 14. These results did not provide a possible explanation for the patient's clinical syndrome.

Eventually, efforts were made to evaluate other medical causes, and an MRI of his brain was ordered. This had to be repeated under general anesthesia due to movement. The MRI completed on 3/26/2025 demonstrated symmetric moderate bilateral anterior cerebral cortical atrophy (including the frontopolar, orbitofrontal, anterior and mesial temporal, anterior cingulate, and insular regions) and associated ex vacuo ventricular dilatation, primarily involving the frontal and temporal horns. Brain parenchyma was normal, and there was no midline shift or mass effect. There was no area of abnormal contrast enhancement. Vascular flow-voids were unremarkable apart from an incidental azygos A2 segment and persistent occipital sinuses. No evidence indicative of acute or recent infarct. The impression by the radiologist was consistent with moderate bilateral anterior cerebral cortical atrophy, presumably due to frontotemporal dementia.

Based on this, lorazepam and valproic acid were discontinued. Genetic testing was also performed, which showed an OPTN variant of uncertain significance, c.377C>A (p.Thr126Asn), but did not find any known pathogenic genetic mutations that are associated with genetic causes of neurodegenerative diseases like Alzheimer's disease and FTD. The patient was started on citalopram for mood symptoms, methylphenidate for impulsivity, and trazodone for sleep. His

partners obtained guardianship, and he was discharged to their care, where his condition has continued to progressively deteriorate

Discussion

This report describes very early-onset FTD in a 33-year-old male patient. While cases of very early-onset FTD have been documented, it is relatively rare in populations under the age of 45.[4] This could presumably lead to it being lower on the differential diagnosis or absent entirely in younger patients. Further, diagnosing FTD can be particularly challenging given its significant overlap with psychiatric conditions and other neurological conditions.[11,12,13]For this reason, knowing potential signs that a patient may have developed FTD is essential.[11] It is also important for providers to understand the criteria for diagnosing FTD, along with knowing the recommended approach to evaluating these patients. [2,17]

In this case, the patient displayed a constellation of symptoms that could individually be explained by several psychiatric or medical conditions. Given his altered mental status and elevated Busch-Francis scores, catatonia was initially considered; however, his minimal response to a lorazepam challenge made this diagnosis less likely. His bizarre behaviors, disorganization, and possible psychotic symptoms raised concern for an underlying thought disorder, though the lack of improvement with multiple antipsychotics suggested another underlying process. Similarly, his repetitive behaviors and prior diagnosis of obsessive-compulsive disorder initially raised concern for severe OCD, but the profound behavioral dysregulation and limited response to serotonergic treatment were atypical for isolated obsessive-compulsive disorder. Collectively, the patient's continued symptomatology with minimal improvement to multiple psychiatric interventions increased the likelihood of an underlying neurodegenerative condition.

The eventual decision was made to evaluate a potential neurological cause of this patient's condition by conducting an MRI of the brain. This case presented a notable barrier to this step in the evaluation, as the patient was unable to follow directions or hold still. This led to the need for the MRI to be repeated under anesthesia. This is important to note as it poses another potential barrier to diagnoses for other patients who may present with similar symptoms in the future. Findings on this MRI were key to the eventual diagnosis of FTD in this patient. This case highlights the importance of considering neurodegenerative diseases in differential diagnoses for patients, even in younger age groups. Further, it demonstrates the need to overcome potential barriers presented by a patient's symptoms that may make necessary tests like MRIs more challenging.

Using the International Consensus Criteria for Behavioral Variant FTD (FTDC), the patient meets criteria for probable bvFTD.[2] Positive symptoms include: clear deterioration of cognition and behavior over time, behavioral disinhibition in the form of impulsive, rash, and careless actions and socially inappropriate behavior, apathy/inertia, and development of simple repetitive movements, ritualistic behaviors, and compulsive behaviors. Furthermore, the patient had a significant functional decline and had MRI results consistent with bvFTD. Lastly, the patient's symptoms were not better explained by any psychiatric, non-degenerative neurological, or medical condition.

Notably, genetic testing on this patient showed no pathogenic genetic mutations that are associated with genetic causes of neurodegenerative diseases like FTD. However, an OPTN variant of uncertain significance was detected. Further consideration for genetic causes of this patient's FTD is of particular interest, considering he has an identical twin, and this twin was noted to have had unspecified personality changes as well. Although this OPTN variant is currently classified as a variant of uncertain significance, future investigation may clarify whether it contributes to this phenotype.

This case highlights several features that should prompt psychiatrists to consider an underlying neurodegenerative disorder despite the patient's young age. Typically, primary psychiatric conditions do not produce a steadily progressive loss of function across multiple domains. Over several years, this patient developed worsening of several psychiatric symptoms along with cognitive impairment, urinary incontinence, disinhibition, stereotyped movements, and ultimately profound loss of independent functioning. Rather than improving with psychiatric treatment and interventions, his symptoms continued to progress. Progressive deterioration across functional, cognitive, and behavioral domains is atypical for primary psychiatric illness and should prompt consideration for a neurodegenerative process. When accompanied by treatment resistance, loss of social boundaries, and marked executive and behavioral dysfunction, early neuroimaging should be strongly considered.

Conclusion:

Even in younger patients, providers should consider neurodegenerative conditions like FTD when they encounter patients with progressive disinhibition, personality changes, and treatment resistance, particularly when accompanied by rapid functional decline. In these patients, careful evaluation of the patient's history is essential. Appropriate evaluation may include neuroimaging, laboratory testing, neuropsychological assessment, and, when indicated, genetic testing. Continued investigation into the genetic mechanisms underlying FTD remains warranted.

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