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SHORT REVIEW

Harnessing Herbal Bioactives for Anxiety Management: A Natural Remedy Perspective

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Abstract

Anxiety disorders are a major global mental health issue that are frequently treated with pharmacological treatments that have a limited long-term efficacy and a risk of side effects. The possibility of bioactive chemicals obtained from plants as natural alternatives for anxiety management is explored in this review. After providing a brief synopsis of the neurological underpinnings of anxiety, emphasizing important neurotransmitter systems and brain regions, we concentrate on phytochemicals with anxiolytic properties, including flavonoids, alkaloids, terpenoids, and phenolics. A variety of therapeutic plants are examined, with a focus on their active ingredients, experimental confirmation using *in vivo* behavioral models, and corroborating data from preclinical and clinical research. These results underline the potential therapeutic benefits of herbal ingredients and the role that phytochemicals play in modifying circuits linked to anxiety. However, standardized clinical procedures and more thorough mechanistic research are necessary for transforming these natural substances into effective therapeutic treatments.

Major Findings: Plant-derived bioactives, particularly flavonoids, alkaloids, terpenoids, and phenolics, show notable anxiolytic effects by modulating neurotransmitter systems. Evidence from studies supports their role in complementary anxiety therapies.

Keywords: Anxiety, Bioactives, Herbal Remedies, Medicinal Plants, Natural anxiolytics, Phytochemicals

Abbreviations: 5-HT-5-Hydroxytryptamine; AMPA-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic; DA-Dopamine;DSM-5-Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; E-Epinephrine; EPM-Elevated Plus Maze; EZM-Elevated Zero Maze; GABA-Gamma-Aminobutyric Acid; HBT-Hole Board Test; LDB-Light/Dark Box;NE-Norepinephrine; NMDA-N-methyl-D-aspartate; OFT-Open Field Test; SERT-Serotonin Reuptake Transporter; SSRIs-Selective Serotonin Reuptake Inhibitors;VMAT2-Vesicular Monoamine Transporter 2

1. Introduction

Psychological conditions encompass a variety of issues that lead to a progressive decline in neural function, such as motor dysfunction and cognitive decline. These conditions are frequently caused by mechanisms such as neuroinflammation and oxidative stress. Mood and anxiety disorders often coexist and affect general quality of life as well as therapeutic results[1,2]. Excessive fear or worry in reaction to perceived dangers, whether generic or situation-specific, is an indicator of anxiety disorders, which are biopsychosocial diseases. Several investigations have already been carried out about the high prevalence of anxiety[3]. Adolescents, who frequently battle with excessive stress and panic, are most affected[4].

One of the main hurdles to treating anxiety disorders is that, even after periods of remission, many individuals are prone to recurrence and do not react to the pharmacological treatments currently available. Thus, the development of efficacious non-pharmacological therapies is imperative[5]. Natural anxiolytics, like herbal medicines and dietary supplements, have gained popularity in recent years since they are thought to be less harmful and have fewer adverse effects. These therapies have been popular in complementary and

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alternative medicine because they provide people, especially those with chronic diseases, with low-risk, affordable remedies[6].

Herbal treatments typically lessen the negative side effects of synthetic anxiolytics, which can include migraines, sexual dysfunction, addiction, seizures, and even suicidal thoughts. Research indicates that, when compared to synthetic treatments, the use of herbal medicines can lessen adverse effects in as many as 45% of cases[7]. A mainstay of conventional medical procedures for a long time, herbal medicine offers a wealth of bioactive substances with potential for therapeutic use. The use of herbal treatments to treat neurological problems has drawn more attention in recent years[8].

Herbal medicine, sometimes referred to as phytomedicine or botanical medicine, has a long history and uses plant parts for therapeutic reasons, including berries, flowers, stems, roots, and leaves[9]. In addition to the active phytochemicals included in these components, plant-based medications may also contain unprocessed or processed plant materials with other components such as solvents, dilutions, or preservatives[10]. According to reports, almost half of the medications that were approved between 1980 and 2009 were made from natural sources, and certain phytochemicals have shown health benefits. Many of these substances are secondary metabolites with anxiolytic qualities, including phenolic acids, alkaloids, flavonoids, saponins, and terpenes[11].

Allelochemicals are a subclass of secondary metabolites that include phenols, alkaloids, terpenes, sugars, glycosides, and derivatives of amino acids, among other bioactive substances. Typical instances include phenolics (such as benzoic acid, vanillic acid, gallic acid, kaempferol, quercetin, and rutin); terpenoids (such as citral, linalool, cymol, ledol, and artemisinin); and nitrogen-containing compounds (such as acetylcholine, histamine, serotonin, dopamine, and noradrenaline)[12].

Many of these are significant phytochemicals with established pharmacological effects related to neurological function, even if not all of them are directly related to anxiety management. With an emphasis on their phytochemical profiles and allelopathic significance, this review attempts to investigate the potential of plant-derived bioactive compounds in the management of anxiety disorders. Through the integration of contemporary pharmacological insights with traditional and phytochemical knowledge, this study aims to present a thorough understanding of how plant molecules can provide safe and effective options for anxiety reduction.

2. Methodology

This review was conducted by systematically searching scientific databases including PubMed, Scopus, and Google Scholar using keywords such as "anxiety," "herbal bioactives", "phytochemicals", "medicinal plants" and "natural anxiolytics". Inclusion criteria comprised English-language articles published in the last few years focusing on preclinical and clinical studies evaluating the anxiolytic potential of herbal bioactive compounds. Exclusion criteria included studies lacking specific data on phytochemicals or their anxiolytic activity. Data were extracted regarding the types of phytochemicals, plant sources, experimental models used, mechanisms of action, and study outcomes.

3. Anxiety and its Neurobiological Targets

Anxiety is a forward-focused emotional condition characterized by feelings of uneasiness, discomfort, and apprehension about a potential or unidentified future threat[13]. It stands as the most common category of mental illness, encompassing disorders such as specific phobias, panic disorder, agoraphobia, social anxiety disorder, and generalized anxiety disorder[14]. In the latest edition of the DSM-5, posttraumatic stress disorder and obsessive-compulsive disorder have been reclassified into separate categories, no longer grouped under anxiety disorders. Meanwhile, selective mutism and separation anxiety disorder, previously more common in pediatric diagnoses, have now been officially recognized as anxiety disorders in adults as well[15]. The concept of anxiety spans both normal emotional reactions to stress and pathological conditions marked by excessive worry or psychological strain[16]. Anxiety disorders arise from imbalances in multiple neurotransmitter systems and their associated

receptors. Because of their crucial involvement in emotional regulation, memory processing, and cognitive functions, several brain regions have been extensively studied to better understand the neurobiological basis of anxiety[17].

3.1 Neurotransmitter and Receptor System Involved

A variety of neurotransmitters and their corresponding receptors, such as GABA, glutamate, NE, serotonin, and DA, are involved in the regulation of anxiety. Each plays a distinct role in shaping emotional responses and anxiety-related behaviors[18]. Anxiety disorders often stem from disruptions within these neurotransmitter systems and their receptor pathways.

The following neurotransmitters and receptors are particularly implicated in anxiety[19]:

3.1.1 Serotonergic System

- Neurotransmitter-Serotonin or 5-HT
- Receptor involved- 5-HT_{1A} heteroreceptors
- Function- Enhancing serotonergic tone (e.g., SSRIs) produces anxiolytic effects by modulating fear, mood, and stress responses.

3.1.2 Dopaminergic System

- Neurotransmitter-DA
- Receptor involved- D_1 and D_2heteroreceptors
- Function-Dysregulation in mesolimbic and mesocortical dopaminergic pathways is associated with anxiety-like behaviors.

3.1.3 Noradrenergic System

- Neurotransmitter-epinephrine(E) and NE
- Receptor involved-α1, α2, and β adrenergic receptors
- Function- Altered noradrenergic signaling, especially low NE levels, contributes to heightened anxiety and stress reactivity.

3.1.4 GABAergic System

- Neurotransmitter-GABA
- Receptorinvolved-$GABA_A$and$GABA_B$heteroreceptors
- Function-enhancing GABAergic transmission reduces neuronal excitability and produces anxiolytic effects.

3.1.5 Glutamatergic System

- Neurotransmitter- Glutamate
- Receptor involved-NMDA and AMPAreceptors
- Function- Excess glutamatergic activity linked to anxiety

3.2 Brain Regions and Circuits Implicated in Anxiety

The medial prefrontal cortex, bed nucleus of the stria terminalis, ventral hippocampus, anterior cingulate cortex, and amygdala have long been central to anxiety research due to their involvement in emotional regulation, memory processing, and cognition. These areas, along with other critical parts including the nuclei, superior and inferior colliculi, and periaqueductal grey matter, have been identified as major contributors to the neurobiological pathways underlying anxiety, depression, and behavioral regulation[20].

4. Bioactive Phytochemicals

Phytochemicals, or phytonutrients, are naturally occurring bioactive compounds in plants that have garnered significant scientific interest due to their medicinal and nutritional potential in human health. Beyond their protective role in plants, they contribute to sensory attributes like color, scent, and taste. Their strong bioactivity against various illnesses, minimal cytotoxic effects, and usefulness in dietary supplement formulations have made them a focal point in research[21]. They are abundantly present in dietary sources like whole grains, legumes, seeds, nuts, fruits, and vegetables. Only a fraction of the tens of thousands of phytochemicals present in nature have been successfully isolated and characterized[22].These secondary metabolites have diverse functionalities, including roles in preventing chronic diseases and promoting overall wellness. Numerous studies have highlighted the therapeutic potential of these bioactive compounds in promoting human well-being[23].

Anxiety arises from Physiological, psychological, and nutritional factors, with nutrition playing a critical role in its onset and progression. Nutrients are essential for hormone regulation and the optimal functioning of neurotransmitters. Owing to their nutritional and phytochemical composition, plant-based foods such

as fruits and vegetables hold significant medicinal value. Their diverse therapeutic effects, which include neuroprotective, immunomodulatory, anti-hypertensive, anti-diabetic, anti-cancer, anxiolytic, and anti-convulsant effects, extend their benefits beyond basic nutrition[24]. Given their rich phytochemical content and long-standing use in traditional healing practices, natural medicinal herbs are increasingly recognized for their role in innovative anxiety management strategies. These plants are abundant in diverse bioactive compounds like polyphenols, terpenes, glycosides, alkaloids, and flavonoids, many of which exhibit neuropharmacological activity and show promise in modulating neurotransmitter systems involved in anxiety disorders[25].

Like synthetic medications, many bioactive phytochemical compounds exert anxiolytic effects by influencing six key neurotransmitter pathways: 5-HT, DA, glutamate, GABA, acetylcholine, and NE. These compounds, primarily derived from alkaloids, terpenoids, and phenolics, have shown promising therapeutic effects in alleviating anxiety symptoms.

Table 1. Overview of phytochemical constituents in medicinal plants with reported anxiolytic action

S. No.	Name of the Plant and Family	Part of the Plant	Extract	Model	Secondary Metabolite Responsible for Activity	References
1	*Azadirachta indica* A. F: *Meliaceae*	Flower	A. indica flower extract	EPM, OFT	Flavonoid - quercetin	35
2	*Bombax costatum* Pellegr. et Vuillet. F: *Bombacaceae*	Roots	Aqueous extract	EPM, HBT, OFT	Alkaloids, triterpenoids, anthraquinones, glycosides, tannins, flavonoids, saponins, and phenols	36
3	*Canarium resiniferum* F: *Burseraceae*	Leaves	Methanol extract	EPM, HBT, LDB	Alkaloids, tannins, phenols, and flavonoids	37
4	*Coriandrum sativum* F: *Apiaceae*	Seeds	Aqueous extract	EPM, LDB	Flavonoids, phenolics, alkaloids, terpenes, steroids	38
5	*Galinsoga parviflora* F: *Asteraceae*	Leaves	Ethanolic extract	HBT, LDB	Alkaloids, flavonoids, sterols, terpenoids	39
6	*Moringa oleifera* Lam. F: *Moringaceae*	Seeds	Water-soluble lectin	EPM, OFT	Lectins	40
7	*Neurada procumbens* Linn F: *Neuradaceae*	Whole plant	Methanolic extract	LDB, EPM, HBT	Flavonoids, phenols, saponins, coumarin, tannins	41
8	*Phoenix dactylifera* F: *Arecaceae*	Fruit	Ethanolic extract	EZM, Marble Burying	Flavonoids and Steroids	42
9	*Salvadora persica* F: *Salvadoraceae*	Stem bark	Aqueous and ethyl acetate extracts	EPM, LDB	Flavonoids, alkaloids, tannins	43
10	*Ziziphus mauritiana* Lam. F: *Rhamnaceae*	Leaves	Chloroform extract	EPM, Mirrored Chamber, LDB	Pentacyclic triterpenoid	44
11	*Psidium guajava* L. F: *Myrtaceae*	Leaves	Ethanolic extract	EPM, LDB	Flavonoids, phenolics, alkaloids, saponins, tannins	45
12	*Annona muricata* L. F: *Annonaceae*	Leaves and Bark	Aqueous and ethanolic extracts	EPM	Flavonoids, alkaloids, tannins, glycosides	46
13	*Cissus adnata* Roxb. F: *Vitaceae*	Whole plant	Methanolic extract	EPM, HBT	Flavonoids, phenols, tannins, saponins, cardiac glycosides	47
14	*Campomanesia pubescens* F: *Myrtaceae*	Fruits	Ethanolic extract	EPM, OFT, Marble Burying	Flavonoids	48
15	*Blumea lacera* F: *Asteraceae*	Leaves	Methanolic extract	EPM, HBT, LDB	Flavonoids, phenolics, thymol, cuminol	49

Human clinical trials have evaluated the efficacy of several plants, including *Humulus lupulus*, *Matricaria chamomilla* L., *Lavandula angustifolia*, and *Aloysia polystachya*[26].

Recent progress in phytochemical analysis and behavioral pharmacology has facilitated the discovery of specific plant-derived compounds with potential anxiolytic properties. For example, flavonoids like apigenin and quercetin[27], alkaloids such as berberine[28] and alstonine[29], terpenoids including linalool[30] and ursolic acid[31], as well as phenolic compounds like gallic acid[32] and coumaric acid[33], have all shown effectiveness in preclinical studies focused on anxiety. These findings underscore the therapeutic relevance of plant-derived molecules and provide a scientific basis for their inclusion in integrative and complementary strategies for anxiety management.

5. Key Plants with Anxiolytic Phytochemicals

Several medicinal plants have demonstrated considerable promise in treating anxiety disorders, largely owing to their content of neuroactive phytochemicals. Key constituents such as Terpenoids, phenolics, flavonoids, and alkaloids produce anxiolytic effects by interacting with central neurotransmitter pathways[34]. The effectiveness of these plant-based extracts has been validated through various *in vivo* models, including the OFT, LDB, EZM, EPM, and HBT Table 1 outlines key medicinal plants investigated for their anxiolytic effects, highlighting the plant parts used, type of extracts, experimental models employed, and key secondary metabolites responsible for the observed effects.

6. Preclinical and Clinical Insights

Emerging indications from both preclinical and clinical investigations support the potential of various herbal agents in modulating anxiety-related behaviors. While the body of research continues to grow, recent findings provide compelling insights into the therapeutic possibilities of these natural substances for anxiety management.

6.1 Preclinical Studies

In preclinical studies, *Psilocybe cubensis* has demonstrated significant anxiolytic effects in mice. Oral and intraperitoneal administration of the whole mushroom and its aqueous/methanolic extracts (1–100 mg/kg) showed anxiolytic responses in the OFT and EPM. These effects were comparable to those of standard drugs, such as buspirone and fluoxetine. No signs of neurotoxicity were observed, and the LD_{50} was more significant than 2000 mg/kg. Chemical analysis verified that psilocybin and psilocin were present, particularly in the aqueous extract, suggesting their role in the observed pharmacological activity[50].

Another preclinical study highlighted the anxiolytic potential of *Sesamum indicum* (sesamol), a phenolic lignan. When given oral sesamol at doses of 25 and 50 mg/kg, adult Swiss albino mice displayed adose-dependent reduction in anxiety-like behaviors. Behavioral assessments included the OFT, swing test, hole cross test, and LDB test. Co-administration with diazepam enhanced anxiolytic effects, while flumazenil reversed them, suggesting $GABA_A$ receptor involvement. Molecular docking showed sesamol interacts with $GABA_A$ receptor α_2 and α_3 subunits, supporting its mechanism of action[51].

Further investigations using zebrafish larvae demonstrated that *Sceletium tortuosum* exhibits dose-dependent anxiolytic-like effects, assessed via the LDB. Among its alkaloid constituents, the anxiolytic response was strongly influenced by mesembrine at physiologically relevant concentrations (12.5 µg/mL), while others showed limited activity. The effects are thought to involve modulation of serotonergic mechanisms, including SERT inhibition and VMAT-2 upregulation. Human-equivalent dosing was used to enhance translational relevance[52].

A study on the hydro-ethanolic leaf extract of *Parquetina nigrescens* investigated the anxiolytic effects in male Wistar rats. Anxiety was induced through an intraperitoneal injection of pentylenetetrazol at 20 milligrams per kilogram, and the extract was administered at doses of 100, 150, and 250 milligrams per kilogram. Significant anxiolytic effects were observed in behavioral assessments such as the EPM and OFT, with the extract demonstrating a dose-dependent anxiolytic effect. Additionally, treatment with the extract improved markers of oxidative stress in the brain, including reductions in malondialdehyde and nitrite levels. These findings suggest that *Parquetina nigrescens* exhibits anxiolytic properties,

possibly through modulation of oxidative stress and neurochemical pathways, thus highlighting its potential as a therapeutic candidate for anxiety disorders[53].

6.2 Clinical Studies

Cannabinoids, especially delta-9-tetrahydrocannabinol and cannabidiol from *Cannabis sativa*, have shown promise in treating anxiety disorders. Clinical and preclinical investigations support their anxiolytic effects and better safety profile in comparison to existing anxiolytics. However, there are currently no FDA-approved cannabinoid-based anxiety treatments available, highlighting the need for further research[54].

In a multicenter, randomized, double-blind, placebo-controlled trial, adults with mild-to-moderate anxiety received 20 mg of EP107™, a standardized *E. angustifolia* extract, twice daily for 7 days. The Hamilton Anxiety Rating Scale and the Hospital Anxiety and Depression Scale-Anxiety subscale were used to measure anxiety. EP107™ significantly reduced the scale scores, especially in items related to psychic anxiety, though the improvements were less pronounced in another scale. There were no significant side effects, and the medication was well tolerated, suggesting EP107™ as a promising natural option for anxiety, meriting further long-term studies[55].

Aframomum melegueta seed extract standardized to 10% vanilloids was tested for its anxiolytic effects in a different randomized, double-blind, placebo-controlled crossover clinical experiment in healthy people with moderate anxiety. For three days, participants were given dosages of 50 mg, 100 mg, or 150 mg every day. The modified Hamilton Anxiety Rating Scale was used to measure anxiety. With no discernible changes in the placebo group, the results demonstrated a significant, dose-dependent decrease in anxiety of 10.27% (50 mg, $p < 0.05$), 25.01% (100 mg, $p < 0.01$), and 37.09% (150 mg, $p < 0.01$). Sleep and happiness also improved without any negative consequences. *In vitro* studies suggest that the extract interacts with key neurobiological pathways associated with anxiety regulation[56].

7. Limitations

Despite promising evidence, the use of herbal bioactives for anxiety management has several limitations.

- There is considerable variability in the phytochemical composition of herbal preparations due to differences in plant species, growing conditions, and extraction methods, leading to inconsistent efficacy across studies[57].
- The lack of standardized dosing and formulation makes it difficult to establish optimal therapeutic regimens[58].
- Potential herb-drug interactions, especially with conventional anxiolytics, may pose safety concerns and require careful consideration in clinical use[59].
- Most studies investigating herbal treatments for anxiety are limited to preclinical or small-scale clinical trials, with a paucity of large-scale, randomized controlled trials to confirm efficacy and safety. Regulatory challenges, coupled with limited pharmacovigilance data, further restrict the integration of herbal medicines into mainstream anxiety management strategies[60].

Addressing these limitations through well-designed studies and standardization efforts is essential for translating the potential of herbal bioactives into effective clinical therapies for anxiety.

8. Future Prospects

Despite promising results from preclinical and clinical research, there are still a number of unaddressed concerns regarding the application of herbal bioactives intreating anxiety. The advancement of standardized formulations, the determination of optimal dosages, and thorough safety evaluations should be the main objectives of future research. Furthermore, large-scale, placebo-controlled clinical trials are essential for validating preclinical findings and assessing efficacy in a range of demographics.

Subsequent research should concentrate on defining the specific molecular targets and pharmacokinetic properties of the diverse range of phytochemicals demonstrating anxiolytic activity. Numerous plant extracts covered in this review exhibit multi-target mechanisms that include anti-inflammatory properties, oxidative stress reduction, and neurotransmitter regulation. Nevertheless, the majority of data are still restricted to animal or *in vitro* models. Well-designed translational studies that correlate laboratory outcomes

with clinical relevance will be necessary to advance the field. The discovery of lead molecules from these bioactives may help developing the standardized, evidence-based herbal treatments for anxiety disorders.

9. Conclusion

Anxiety disorders are multifaceted and intricate, involving brain circuitry and neurotransmitter dysregulation. While traditional pharmacological therapies may offer effectiveness, they are often linked to side effects and limited therapeutic scope. Plant-based therapies, which provide a safer and more comprehensive option, have gained popularity as a result. By interacting with important neurotransmitter pathways, phytochemicals like terpenoids, phenolics, alkaloids, and flavonoids have shown significant anxiolytic effects. Preclinical and clinical data support the incorporation of certain medicinal plants into supplemental treatment approaches by highlighting their ability to lessen anxiety symptoms. Their relevance in both traditional medicine and contemporary drug discovery is shown by the wide pharmacological variety of these chemical compounds.

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11. Author Contribution

Conceptualization and design, A.M. and B.P.; methodology, M.; formal analysis, A.M. and M.; investigation, M.; resources, M.; data curation, M.; writing—original draft preparation, M.; writing—review and editing, M.; visualization, M., A.M., and B.P.; supervision, M., A.M., and B.P. All authors have read and agreed to the published version of the manuscript.

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