

Plant-Derived Psychotropic Agents Targeting Neurotransmitter Systems: Pharmacognostic Evidence, Mechanisms, and Clinical Relevance

Nicky Jaiswal^{1*}, Kabhi Khanna², Shah Samreen², Priyanka Singh³, Rifat Siraj³

Abstract

Psychiatric health problems are also a large burden on global health and existing psychotropic drugs may be restricted by relative effectiveness, side effects, and inadequate long-term tolerability. Plant-based psychotropic agents have subsequently been the focus of interest in the form of complementary or alternative therapies. This review outlines the pharmacognostic, mechanisms of action and therapeutic importance of plant-based psychotropic agents against central neurotransmitter systems. The traditional medicinal practices give a lot of information on how botanicals can be used to treat mood disorders, mental anxiety, insomnia and intellectual incapacity. Preclinical evidence reveals that phytochemicals including alkaloids, flavonoids, terpenoids and phenolic compounds regulate serotonergic, dopaminergic, GABAergic and glutamatergic systems and also have neuroprotective and anti-inflammatory effects. The new clinical evidence shows some promise in psychiatric conditions of mild to moderate severity with relatively positive safety and tolerability rates. Nevertheless, issues associated with standardization, dose optimization, herb–drug interactions, and translation restrictions remain. Strict research and clinical validation could help to solve these problems and allow incorporating plant-derived psychotropic agents into the realm of contemporary psychiatry.

Keywords: Medicinal plants, neurotransmitter systems, pharmacognosy, phytochemicals, plant-derived psychotropic agents

INTRODUCTION

Psychiatric disorders constitute one of the biggest and growing health issues worldwide that cause high disability rates, diminished quality of life, and socioeconomic loss in all segments of the population, especially among adolescents and working-age adults. Although there has been progress in terms of awareness and clinical care about mental health, there still remains a significant number of people with mental health issues like depression, anxiety disorders, schizophrenia, and bipolar disorders who are not

properly treated or managed because of stigma, poor access to health care and limited resources. In most cases, including those where treatment is present, the existing therapy regimens usually do not result in full or permanent remission [1]. As much as conventional psychotropic drugs have worked with many patients, they are characterized by significant drawbacks such as partial efficacy, slow action, resistance to treatment, and a whole suite of adverse effects such as sedation, metabolic dysfunctions, impaired cognition, extrapyramidal, and sexual dysfunction. They often undermine patient compliance and precondition polypharmacy, thus exposing patients to drug–drug interactions and chronic toxicity. As a result, safer, and more effective and better tolerated therapeutic options that can respond to multifactorial and complex pathophysiology of psychiatric disorders are urgently required. In this regard,

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psychotropic agents of plant origin have become the subject of new scientific attention because of long history of use in folk medicine to treat mood disorders, anxiety, insomnia, and cognitive impairment [2]. There are vast sources of structurally diverse phytochemicals in medicinal plants, many of which have multimodal activity, e.g., modulation of key neurotransmitter systems, antioxidant, and anti-inflammatory effects and neuroprotective activities. Recent breakthroughs in pharmacognosy, phytochemical standardization, and the recent trends in drug-delivery systems have reinforced the translational prospective of these natural compounds, making plant-based psychotropic agents promising complementary or alternative agents to seal the current therapeutic gaps in psychiatric care [3].

PSYCHOTROPIC AGENTS AND NEUROTRANSMITTER SYSTEMS

The psychotropic agents are a heterogeneous group of compounds which show therapeutic effects by altering brain activity, mood, cognition, and behavior by acting on central nervous system pathways and are often categorized into antidepressants, antipsychotics, anxiolytics, mood stabilizers, and sedative–hypnotics according to their main clinical uses. The common uses of antidepressants are in depression and anxiety disorders, antipsychotics in psychotic disorders, including schizophrenia and bipolar disorder, anxiolytics in anxiety disorders, mood stabilizers in affective disorders, and sedative–hypnotics in sleeping disorders [4]. Most of the traditional psychotropic drugs are synthetic, and in most cases, they have a narrow profile with only a few molecular targets, but the plant psychotropic agents have a wider pharmacological profile, which affects more than one neural pathway at once. This attribute is so because psychiatric disorders are multifactorial as well and entail intricate dysregulation in numerous interconnected neurotransmitter systems. Neurotransmitters are central to mental health, and their synthesis, release, receptor functioning, or reuptake has a significant relation to psychiatric symptoms [5]. Serotonergic system mainly controls mood, emotion, and anxiety, and the dopaminergic controls motivation, reward, cognition, and development of psychotic characteristics. Both gamma-aminobutyric acid (GABA) system as the main inhibitory circuit in the brain plays a vital role in the regulation of anxiety, stress reactions, and sleep, and the glutamatergic system is the major excitatory system that is becoming more associated with depression, cognitive deficiencies, and neuroplasticity impairment. Based on Figure 1, the plant-derived psychotropic agents can alter these major neurotransmitter systems in a variety of mechanisms including receptor interaction, regulation of neurotransmitter release or uptake, as well as indirect neuroprotective actions. This is the therapeutic attribute of most medicinal plants whose antidepressant, anxiolytic, antipsychotic, and mood-stabilizing effects are mediated by the capability to influence serotonergic, dopaminergic, GABAergic, and glutamatergic systems in an integrated manner and helps justify its possible role in the treatment of psychiatric disorders [6].

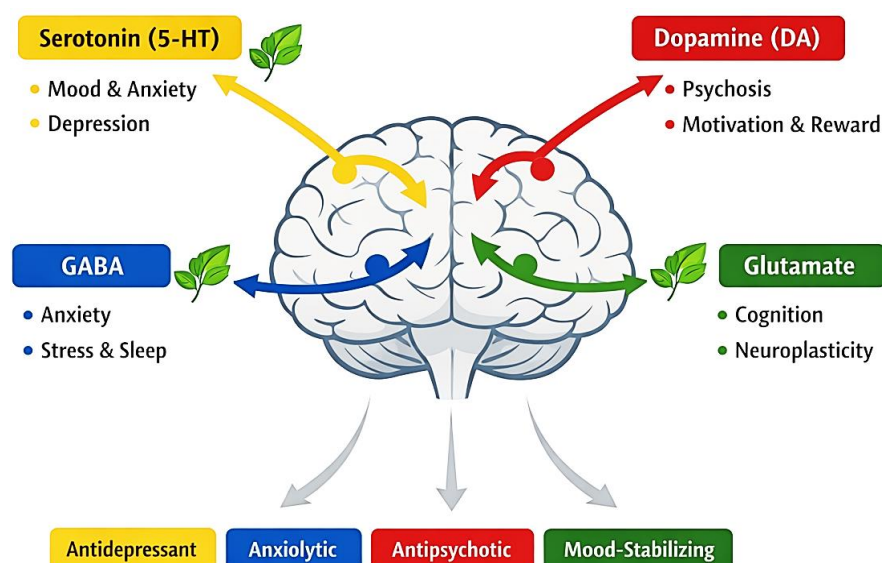


Figure 1. Major neurotransmitter systems involved psychiatric disorders and their modulation by plant-derived psychotropic agents.

PHARMACOGNOSTIC EVIDENCE OF PLANT-DERIVED PSYCHOTROPIC AGENTS

Ethnopharmacological experience has been instrumental in discovering psychotropic medicinal plants as botanical medicines are historically utilized throughout all parts of the world to treat mental and emotional disorders like anxiety, depression, insomnia, mental impairment, and psychosis. They are systems such as Ayurveda, Traditional Chinese Medicine, Unani medicine and other traditional indigenous systems that focus on holistic treatment where the mental health is strongly related to the total physiological equilibrium. These practices have continually provided valuable leads to the use of certain plants as nervine tonics, sedatives or mood stimulators, in modern pharmacognostic studies [7]. The efficacy of these plants in the treatment process depends highly on the parts of the plant to be used, and the traditional preparations in which the plant is used. The use of leaves, roots, rhizomes, bark, seeds, and flowers are selective based on the phytochemical composition of each, and classical preparations, including decoctions, infusion, powders, tinctures, and polyherbal formulations, are crafted to be more effective in terms of extraction, bioavailability, and therapeutic effects. Based on pharmacognostic, standardization, quality control and reproducibility entail the understanding of the selection and methodologies used in formulations of part of plants [8].

These medicinal plants have a psychotropic effect mainly due to classes of phytochemicals such as alkaloids, flavonoids, terpenoids, phenolic compounds and glycoside which act upon multiple central nervous system targets in a variety of different ways. These compounds regulate major neurotransmitter systems, such as serotonergic, dopaminergic, GABAergic, and glutamatergic systems and their action is usually multimodal and is in line with complex neurobiology of psychiatric conditions. As described in Table 1, several medicinal plants exhibit definite correlations between traditional medicine, plant components, main class of phytochemicals, and targeted neurotransmitter systems, which demonstrate their therapeutic potential. Such synergies of ethnopharmacological data with phytochemical and neuropharmacological are the factors behind the increasing research attention to plant-based psychotropic agents as potential complementary or alternative interventions in mental health care [9].

Table 1. Medicinal plants with psychotropic activity, major phytochemicals, and targeted neurotransmitter systems.

Medicinal plant	Family	Plant part used	Major phytochemical classes	Targeted neurotransmitter system(s)	Reported psychotropic effect
<i>Withania somnifera</i>	Solanaceae	Roots	Withanolides, alkaloids	GABAergic, serotonergic	Anxiolytic, antidepressant.
<i>Bacopa monnieri</i>	Plantaginaceae	Whole plant	Bacosides, flavonoids	Serotonergic, cholinergic	Cognitive enhancement, antidepressant.
<i>Hypericum perforatum</i>	Hypericaceae	Aerial parts	Flavonoids, naphthodianthrones	Serotonergic, dopaminergic	Antidepressant.
<i>Valeriana officinalis</i>	Caprifoliaceae	Roots, rhizomes	Valerenic acids, terpenoids	GABAergic	Sedative, anxiolytic.
<i>Passiflora incarnata</i>	Passifloraceae	Aerial parts	Flavonoids, alkaloids	GABAergic	Anxiolytic, sedative.
<i>Panax ginseng</i>	Araliaceae	Roots	Ginsenosides (saponins)	Dopaminergic, glutamatergic	Mood modulation, cognitive enhancement.
<i>Centella asiatica</i>	Apiaceae	Leaves	Triterpenoids, phenolics	GABAergic, serotonergic	Anxiolytic, neuroprotective.
<i>Melissa officinalis</i>	Lamiaceae	Leaves	Phenolic acids, flavonoids	GABAergic	Anxiolytic, mood-stabilizing.

NEUROTRANSMITTER-TARGETED MECHANISMS OF ACTION

Plant-based psychotropic drugs have their mechanism of action by acting on central neurotransmitter systems in a wide, but non-random way, to fill the complicated neurobiology of psychiatric disorders. Serotonergic system is directly associated to mood, emotional stability, anxiety, and stress responses and the plant-based compounds may interfere with the processes of synthesizing serotonin, activating serotonin receptors, and synaptic availability which may result in antidepressant and anxiolytic [3]. Simultaneously, dopaminergic regulation plays a vital role in motivation, reward processing, cognition,

and psychotic symptoms and can be stabilized by phytochemicals, which can regulate dopamine signaling via balanced receptor modulation maintenance and neuroprotective property, suppressing psychosis and mood dysregulation with minimal adverse effects. Increase in GABAergic neurotransmitter is another important mechanism because GABA is the main neurotransmitter involved in inhibition of the brain and is the main neurotransmitter in the brain that regulates the neuronal excitability, anxiety, and sleep [10]. Numerous natural agents based on plants augment GABAergic activity through alteration of receptor behavior, augmentation of neurotransmitter levels, and prevention of damage of inhibitory neurons caused by stress, resulting in anxiolytic and sedative activity with enhanced tolerability. Moreover, the glutamatergic system, a system that controls excitatory signaling, cognition, and synaptic plasticity, is becoming one of the therapeutic targets of depression and schizophrenia. Plant-based psychotropic agents have the potential to control the glutamate release and receptor activity to help prevent excitotoxicity and promote neuroplasticity and cognitive functioning [3]. The mechanistic route of action of the plant-derived psychotropic agents includes phytochemical extraction and subsequent interaction of the extract with various neurotransmitter systems leading to the simultaneous regulation of serotonergic, dopaminergic, GABAergic, and glutamatergic pathways as shown in Figure 2. This multimodal neurotransmitter targeting is indicative of holistic properties of plant-derived compounds and gives a great pharmacological explanation of their possible applicability as complementary or alternative therapies in the treatment of complex psychiatric ailments [11].

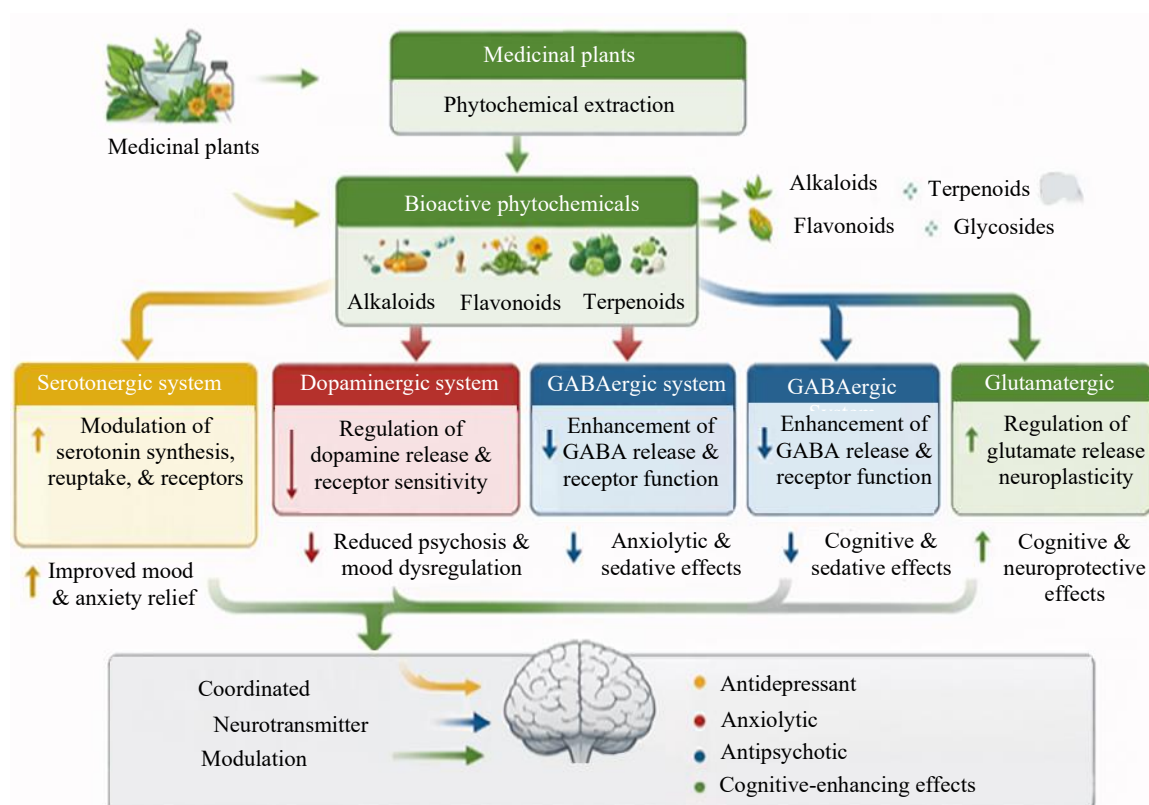


Figure 2. Mechanistic pathway of plant-derived psychotropic agents acting on central neurotransmitter systems.

PRECLINICAL EVIDENCE

The preclinical evidence of the psychotropic potential of plant-derived agents offers imperative support by relating the molecular processes to the functional outcomes of *in vitro* and *in vivo* studies. Plant-derived compounds *In vitro* studies provide a fundamental preliminary platform for testing the neuropharmacological activity of plant-derived compounds in controlled settings, including neuronal cell lines, primary cultures, receptor-based assays, to determine interactions with serotonergic, dopaminergic, GABAergic, and glutamatergic systems [12]. These studies allow the study of binding receptors, neurotransmitter uptake or release, inhibition of enzymes and intracellular signaling patterns in

considerable detail and also define antioxidants, anti-inflammatory, and neuroprotective functions that are becoming more clearly pertinent to psychiatric diseases. In addition to these results, *in vivo* animal models give a more interactive picture of psychotropic actions in whole biological systems, capable of measuring pharmacokinetics, bioavailability, blood brain barrier permeation, and dose response associations. The most common rodent models are applied in testing antidepressant, anxiolytic, antipsychotic, and cognitive-enhancing activities with validated behavioral paradigms that mirror human psychiatric behavior [13]. Functional evidence of therapeutic efficacy is provided in behavioral outcomes in these models including lower levels of anxiety like behavior, better coping with stress, better cognitive performance and normalization of locomotor activity. Such behavioral changes are also supported by neurochemical studies which show that the major neurotransmitters, such as serotonin, dopamine, GABA, and glutamate, are modulated in the appropriate areas of the brain [14]. Further evaluation of oxidative stress parameters, inflammatory mediators, and neurotrophic factors would give an understanding of secondary mechanisms that can lead to enduring benefits. Combined in the integrated way *in vitro*, *in vivo*, behavioral, and neurochemical data enhance the translational performance of preclinical studies and promote the progress of promising plant-based psychotropic agents to clinical assessment [15].

CLINICAL EVIDENCE AND THERAPEUTIC RELEVANCE

Clinical evidence is an important tool in determining the therapeutic relevance of the plant-derived psychotropic agents, and human clinical trials are a direct indicator of their efficacy, safety as well as translation capability. Clinical trials have been conducted on standardized plant extracts, individual phytochemicals and traditional preparations in depression, anxiety disorders, insomnia, and cognitive impairment and the validity of clinical scales has been used to determine the severity of symptoms, functional, and quality of life [3]. Even though study design, sample size, dosage, and formulation variability is still a drawback, numerous studies show significant changes in psychiatric symptoms that are generally consistent with preclinical results. According to the summary in Table 2, the consistency of preclinical mechanisms and clinical outcomes is an indication of the biological consistency of these therapies. According to comparative assessments, although conventional psychotropic medications may be quicker in providing remedy to the symptoms by affecting specified neurotransmitter functions, they are commonly linked with suboptimal remission and severe side effects [16].

Table 2. Comparison of preclinical and clinical evidence of plant-derived psychotropic agents

Parameter	Preclinical evidence	Clinical evidence
Study models	In vitro assays, animal models	Human clinical trials.
Primary outcomes	Neurotransmitter modulation, neuroprotection	Symptom reduction, quality of life.
Behavioral assessment	Anxiety-, depression-, cognition-related tests	Standardized psychiatric rating scales.
Mechanistic insight	High (molecular and cellular pathways)	Moderate (clinical correlation).
Onset of effect	Observable in controlled conditions	Generally gradual.
Efficacy	Strong biological plausibility	Moderate to good (mild–moderate disorders).
Safety data	Toxicity and dose-range evaluation	Tolerability and adverse-effect monitoring.
Limitations	Limited translatability	Small sample sizes, variability.
Overall relevance	Mechanistic foundation	Therapeutic applicability.

Plant-derived psychotropic agents, by contrast, have a slower onset, have multimodal advantages, which may be especially useful in mild to moderate psychiatric disorders and as adjunctive therapies. The evidence synthesized in Table 2 indicates that plant-based agents prove to be as efficient as traditional medications in specific situations and have the benefit of neuroprotective and stress-regulating properties [17]. Their clinical attraction can also be increased by safety and tolerability, whereby plant-based psychotropic agents are more likely to have fewer and less serious adverse events, reduced dependence potential and better long-term tolerance. However, the issues of herb–drug interactions, phytochemical variability, and strict standardization are also important. On balance, the clinical evidence reviewed in Table 2 facilitates the fact that plant-derived psychotropic agents could be used as a complementary or alternative therapy in mental health, especially in long-term treatment and intolerant patients of conventional pharmacotherapy [3].

SAFETY, TOXICITY, AND HERB–DRUG INTERACTIONS

The clinical use of plant-derived psychotropic agents requires safety, toxicity, and herb–drug interactions that are well-considered more so as these agents have become more popular as complementary or alternative therapies. Even though these agents are thought to be safe because of their natural origin, their adverse effects and toxicity issues may occur based on the type of plant species, dosage, formulation, length of their use and whether the person is susceptible or not [18]. The adverse effects detected are usually mild in nature, which include gastrointestinal issues, headache, dizziness, and temporary sedation, but excess or inappropriate use can lead to more severe effects like hepatotoxicity, neurotoxicity or cardiovascular effects. The phytochemical composition varies between plant parts, geographic origin, growing environment, and extracting procedures, which can have a considerable impact on the safety profiles, and with contamination or adulteration, the toxicity increases further [19]. Plant-obtained psychotropic agents have often been found to be advantageous to use over a long period of time because of reduced risks in dependence, tolerance, and adverse effects in comparison to most conventional psychotropic medications, but even in long-term use, plant-obtained psychotropic agents may accumulate toxicity, or cause changes in metabolic activity or physiologic adaptation, especially when they are not used in a standardized manner or monitored in clinical practice. The other significant safety issue is associated with contacts with synthetic psychotropic drugs [20]. The mechanisms by which herb–drug interactions can take place can either be pharmacokinetic, where the drug-metabolizing enzymes are modulated, or pharmacodynamic, where the effect is additive or synergistic on the central neurotransmitter systems. These interactions may change the drug plasma concentrations, decrease the efficacy of the therapy, or decrease the risk of adverse effects, such as excessive sedation or neurotoxicity. Since patients could utilize herbal products unaware of healthcare professionals, active clinical investigation, pharmacovigilance, standardized formulations, and patient education would be critical in promoting successful incorporation of plant-based psychotropic drugs in mental health care [21].

CHALLENGES AND RESEARCH GAPS

Currently, there are multiple interconnected issues and gaps in the literature researching plant-derived psychotropic agents, which require attention to increase their therapeutic potential and translate clinical results into clinical practice. Standardization and quality control is one of the greatest problems because herbal products are usually highly variable in terms of phytochemical composition because of variations in plant species, geographical origin, conditions of their cultivation, harvesting time, parts of plants used, and processing. Poor botanical validation, inconsistency of extraction processes and chances of contamination or adulteration also undermine the quality of the products, safety, and reproducibility [19]. The formulation and dose optimization are also significant research gaps because traditional dosing practices are highly empirical and may not necessarily conform with the current pharmacological guidelines. Diverse bioactive constituents make it difficult to perform dose-response evaluation, poor solubility, poor stability, and low bioavailability of most phytochemicals lower drug efficacy. Higher formulation methods and scientific pharmacokinetic research are thus needed to set up evidence-based dosage regimens and enhance delivery to the central nervous system [22]. Moreover, there are severe limitations in translating research findings to the clinical environment. Although useful to provide mechanical understanding, the preclinical models do not adequately model the human psychiatric ailment and the lack of alignment in metabolism and illness phenotype can constrain clinical forecasting. Moreover, preclinical research often involves homogenized extracts or isolates which are not identical to the clinically used preparations, whereas human trials are typically small, short-term and heterogeneous methodologically [23]. More barriers to clinical development include regulatory difficulties, financial constraints, and intellectual property. These problems can be solved by implementing strict standardization, optimization of formulation, solid translational models, and carefully designed clinical trials to achieve the maximum therapeutic potential of plant-derived psychotropic drugs in the current mental health services [24].

FUTURE PERSPECTIVES AND DRUG DEVELOPMENT OPPORTUNITIES

The future outlook for developing plant-based psychotropic compounds reveals that there are considerable prospects in advancing phytochemical discovery, formulation science, and clinical integration. Development of new psychotropic phytochemicals has become a primary focus, as medicinal plants are a vast and little-explored source of structural diversity of compounds that can take a transistor role in the complex central

nervous systems pathways. Ethnopharmacological knowledge can be used as a good starting point in this process because it helps in the choice of plants that have been traditionally used to treat the mental conditions [25]. As shown in Figure 3, this translational route starts with conventional usage and goes through botanical authentication, phytochemical profiling, and pharmacological screening, to discover bioactive compounds. Metabolomics, high-throughput screening, and computational modeling advances have helped a great deal in enhancing the efficiency of the process of identifying phytochemicals that have multitarget activity in psychiatric diseases [26]. Having discovered them, the sophisticated delivery methods and formulation approaches are important towards converting them into therapeutic agents. Due to poor solubility, low stability and bioavailability, many phytochemicals have limited therapeutic potential and thus new formulation strategies are necessary to improve the delivery of central nervous system, better pharmacokinetic properties and reliability of dosage. Prepared extracts and ideal dosage forms also contribute to regulatory acceptance and adherence by patients [27]. Finally, to ensure that plant-derived psychotropic agents are successfully integrated into modern psychiatry, the following steps need to be accomplished: the translation of the study needs to be completed by passing through the stages of rigorous preclinical validation, well-designed clinical testing, and transparent regulatory frameworks. Such agents are especially convenient as either complementary or adjunctive agents with multimodal mechanisms, enhanced tolerability, and possible ability to develop personalized treatment options. As interdisciplinary studies and clinical acceptance of plant-derived psychotropic agents continue, they might be important constituents of mental health care in the future [28].

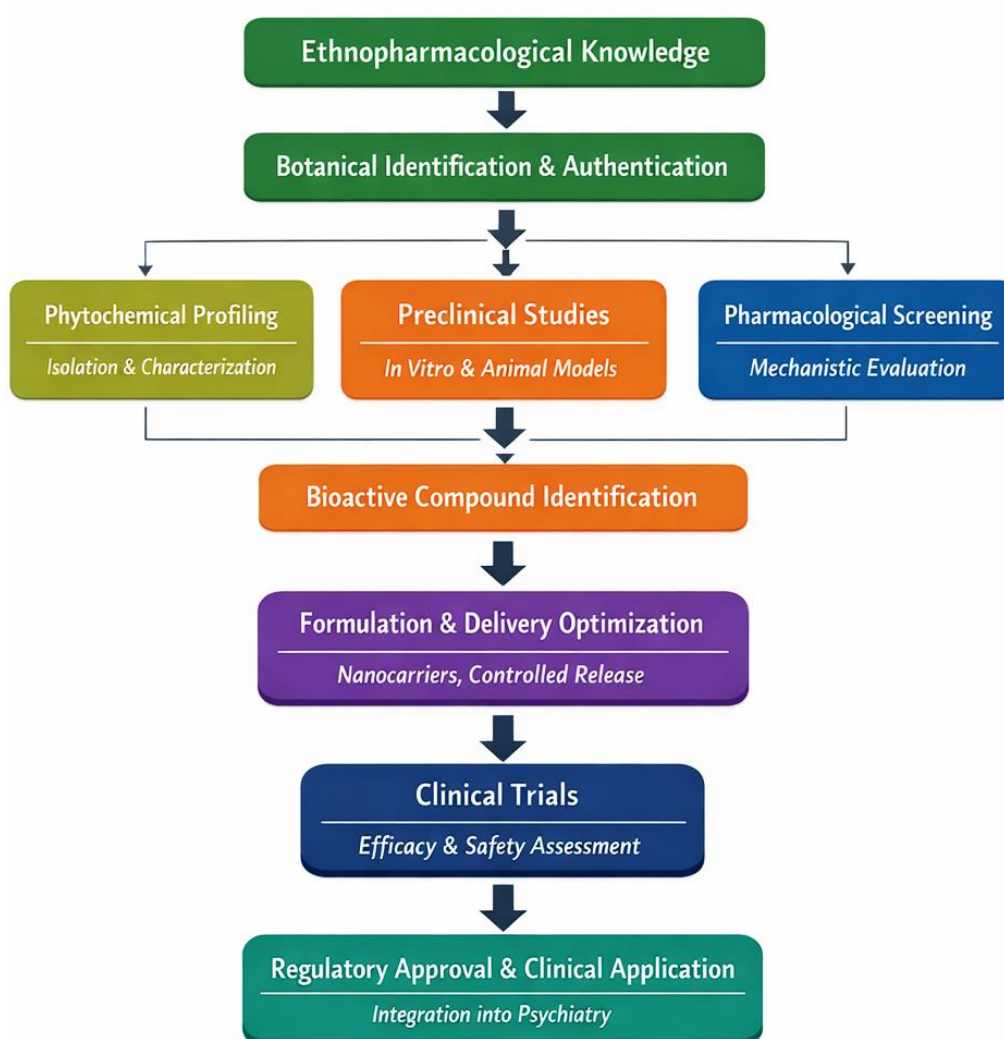


Figure 3. Translational pathway from ethnopharmacology to clinical application of plant-derived psychotropic agents.

CONCLUSION

Plant-based psychotropic drugs are a prospective and scientifically plausible way of treating the multifactorial and complex nature of psychiatric conditions. The growing pharmacognostic, preclinical, and clinical data indicates that medicinal plants and bioactive phytochemicals have the potential for altering the activity of major neurotransmitter networks, such as serotonergic, dopaminergic, GABAergic, and glutamatergic networks, leading to the antidepressant, anxiolytic, antipsychotic, and mood-stabilizing effects. Contrary to most traditional psychotropic medications, which focus on individual pathways, the actions of plant-based agents tend to be multimodal, which can lead to a high level of tolerability and longer-term treatment effects. Ethnopharmacological experience has been of key significance in informing the process of identifying psychotropic plants, and developments in analytical methods, formulation research and translational research have enhanced the scientific foundation on which they have been used in clinical practices. However, any issues surrounding the standardization, dose maximization, long-term safety and interactions between herbs and drugs must be well tackled so that they can be used safely and effectively. To overcome the gap between conventional medicine and contemporary psychiatry the bridging between the two needs effective clinical trials, stringent quality control and definitive regulatory frameworks. In general, psychotropic agents of plant origin have very promising prospects as an adjunct or complement medicine in mental disorders, especially in the long-term treatment and when using them with intolerant patients of traditional pharmacotherapy. Their potential to fully achieve their therapeutic value will continue to be achieved through interdisciplinary research and clinical integration.

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