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**Review Paper**

# A Review of Herbal Medicines for Psychiatric Disorders

**Rohit Karne***

*Research Scholar, Department of Pharmacology, Pravara Rural College of Pharmacy, Loni, Ahilyanagar, Maharashtra, India- 431736*

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## ABSTRACT

**Objective**: St. John's wort, kava, ginkgo biloba, and valerian are herbs that are frequently used to treat mental health issues. **Methods**: Articles about the use of herbs in psychiatry published after 1990 were found by Searching Medline. Sources cited in publications retrieved from The Medline search were analyzed in a secondary search. **Results**: Out of nine standardized and controlled trials, five demonstrated that St. John's wort was more effective than a placebo, while four found no difference in effectiveness when compared to antidepressant medications. It is unknown which components are pharmacologically active. Although kava has been shown to be effective as an anxiolytic in a number of double-blind, placebo-controlled trials, these studies had limited sample sizes, short treatment durations, and poorly defined patient populations. Ginkgo extracts have been used in 40 controlled trials to treat dementia, and all but one of them report clinically significant improvements in memory loss, focus, fatigue, anxiety, and depression. The majority of gingko research used nonstandard metrics, had small sample sizes, and poorly characterized patient populations. Gingko dramatically reduced cognitive function decline in dementia patients, according to a new well-designed multicenter study. Valerian has been demonstrated to increase subjective sleep quality and reduce nocturnal awakenings and sleep latency; however, some studies showed significant placebo effects, and in other cases, the positive effects did not manifest until two to four weeks into the course of treatment.

## INTRODUCTION

**Editor's Note:** The second in a sporadic series of papers about discovered that some significant subjects need more in-depth examination than can be achieved in the comparatively little space of a column, requested the papers. See pages 627–633 of the May 2000 edition for the first article in this series, which examined the pharmacology of depression in children and adolescents. One will

***Corresponding Author:** Rohit Karne
**Address:** *Research Scholar, Department of Pharmacology, Pravara Rural College of Pharmacy, Loni, Ahilyanagar, Maharashtra, India- 431736*
**Email** ✉: karnerohit20@gmail.com

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focus on attention-deficit hyperactivity disorder across all age groups. Herbal goods are widely available in pharmacies and supermarkets, and the $4 billion herbal remedies industry was once considered a counterculture phenomenon (1). According to estimates, 50 million Americans use herbal treatments each month (2), and one in three Americans have used them (1). Psychiatric symptoms are the fastest-growing section of the herbal product industry, and four of the 12 most popular herbal medications—valerian, ginkgo, kava, and St. John's wort are used to prevent or treat these symptoms (1). Herbal goods are widely available in pharmacies and supermarkets, and the $4 billion herbal remedies industry was once considered a counterculture phenomenon (1). One in three Americans is believed to have used herbal treatments (1) The growing popularity of herbal medicines among patients has made it necessary for psychiatrists and other mental health practitioners to learn about the risks, adverse effects, and contraindications of more widely used plants. This subject is regrettably not addressed in the majority of medical school courses, psychiatry residency programs, or textbooks on psychiatry and psychopharmacology. However, as demonstrated by a recent issue of JAMA devoted to alternative medicine (November 11, 1998), this is starting to change. Our review is meant to serve as a concise overview of the topic. A number of current works and publications are recommended to readers for additional information (3,4,5,6,7)

## METHOD:

We looked via MEDLINE for papers about the use of herbs in psychiatry that were published after 1990. Herb, herbal, kava, valerian, gingko, and St. John's wort were the search phrases utilized. Recent herbal medicine textbooks were consulted, and references from papers found by the MEDLINE search were used to conduct a secondary search.

## RESULT:

### St. John's wort

The fragrant perennial St. John's wort (Hypericum perforatum) is indigenous to Europe but is now growing wild in Asia, North America, and South America. Its application dates back to the writings of Hippocrates and Galen, two ancient Greek physicians. In Germany, it has grown to be the second most popular herbal cure in the last 10 years (3) and is now used four times more frequently to treat depression than the most widely prescribed antidepressant (8). St. John’s wort is the second most popular herbal product in the United States. According to estimates, 17% of Americans have consumed goods made with St. John's wort (1). In the United States and other English-speaking nations, St. John's wort gained a lot of popularity when a review article by Linde and colleagues (9) was published in the British Medical Journal in 1996. In the lay press, the article was widely publicized (8,10). Hypericum extracts have been the subject of more than two dozen published reports of clinical trials; most of these investigations have used methanol extracts of the herb (3,9,11). Nevertheless, nine studies are relevant if the analysis is limited to well-monitored trials with defined doses and outcome measurements (3). In five of them, 900 mg daily of an aqueous methanol extract known as LI 160 was used in placebo-controlled trials for a minimum of four weeks of treatment. The Hamilton Rating Scale for Depression (HAMD) was employed as an outcome measure in the five studies (3) (12). In general, HAMD scores improved marginally more in patients who received the extract than in those who received a placebo. When HAMD scores decreased by 50%, 61% of patients who received the extract responded, compared to 24% who received a placebo. For individuals with mild to moderate depression, four investigations using St. John's

wort compared low dosages of maprotiline, imipramine, and amitriptyline with a daily dosage of 900 mg of the LI 160 formulation of hypericum (13,14,15,16). The studies were tiny, which increases the risk of type II error, and there were no placebo control groups, which asked whether the traditional antidepressants were any more effective than a placebo at the dosages employed, even though no statistically significant differences in response were discovered. A multisite study comparing the LI 160 formulation with sertraline and a placebo in an eight-week trial was recently funded by the National Institutes of Health because of the comparatively limited number of well-controlled trials on St. John's wort. Two to three years should pass before results are available placebo in an eight-week trial was recently funded by the National Institutes of Health because of the comparatively limited number of well-controlled trials on St. John's wort. Two to three years should pass before results are available. It is uncertain which ingredients in hypericum extracts might have antidepressant properties. Numerous chemicals can be found in St. John's wort extracts (3,17), and while hypericin is sometimes thought to be the active component, this has not been demonstrated. Additionally, the mode of action is not quite evident. Although extracts of St. John's wort were thought to inhibit monoamine oxidase in early research (18), more recent investigations have not found this inhibition at tissue concentrations that follow standard dosages (19,20). Rather, the extract seems to downregulate serotonin receptors and prevent norepinephrine and serotonin from being reabsorbed (21). Hypericum extracts seldom cause serious side effects. A study of over 3,000 hypericum users found that just 2.4% experienced adverse effects, mostly gastrointestinal distress and allergic responses (22). Headache, sedation, and dry mouth are other adverse effects that have been documented (16). At dosages greater than those commonly used to treat depression, photosensitivity seems to be a concern (23). Cardiac conduction does not seem to be much impaired (24). Due to insufficient safety data, hypericum extract use is not advised during pregnancy or breastfeeding (25) Since hypericum extracts may work by blocking serotonin reuptake, they should not be taken with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, since this could result in serotonin syndrome (26). Furthermore, olanzapine and hypericum extracts have been shown to interact; one patient experienced a 300 percent rise in olanzapine levels following the commencement of St. John's wort (27). The extract's ability to inhibit CYP 1A2 and so disrupt olanzapine metabolism may have been the cause of the latter interaction.

**Kava**

Native to Polynesia and the Pacific Islands, the kava shrub (Piper methysticum) has long been consumed by Pacific Islanders as a beverage made with coconut milk and water (3). In the United States, kava is quickly gaining popularity as a natural product (1). The majority of therapeutic forms are extracts of ethanol and water or acetone and water (3) Only a few herbal medicines have a known pharmacologically active component, such as kava. Meyer (28) demonstrated that the kavapyrones, which in animal models function as muscle relaxants and anticonvulsants, guard against strychnine poisoning and lessen limbic system excitability, are responsible for the effects of kava. Since the kavapyrones have several activities, including blocking norepinephrine reuptake, boosting GABAA receptor densities, inhibiting voltage-dependent sodium channels, and reducing glutamate release, it is unclear exactly how they produce these effects (29,30,31,32) In many double-blind, placebo-controlled studies, a standardized extract including 70% kavapyrones was administered at a daily dose

of 210 mg (3). A significant difference in Hamilton Anxiety Rating Scale (HAMA) scores was observed after just one week of treatment in two of these studies; in the third and largest study, a significant difference in HAMA scores was observed after eight weeks, and the difference persisted until the study's conclusion at week 25 (3). DL-kawain, one of the kavapyrones, has also been shown in many double-blind studies to be more beneficial than a placebo when taken at 200–600 mg daily, as indicated by lower HAMA scores (3) Their inadequately defined patient populations have been the most important critique leveled at any of these studies. Many of them also had brief durations and limited sample sizes. Although kava extracts seem to have anxiolytic qualities, it is unclear which patients would benefit from them the most and how effective they are in comparison to traditional anxiolytics. There have been a few negative effects linked to kava when consumed in quantities between 100 and 210 mg of kavapyrones per day. According to research comparing kava with oxazepam, kava does not seem to hurt mental clarity, cognitive function, or coordination (34, 35). However, ataxia (36), mild morning fatigue, and decreased reaction when driving have been documented (4). Rarely, kava may cause gastrointestinal issues, allergic responses, skin discoloration or scaling, pupil dilatation, and blurred vision (4,34). Hepatotoxicity, hematuria, macrocytic anemia, ataxia, elevated patellar reflexes, weight loss, hair loss, and rash have all been linked to heavy use by Pacific Islanders and Australian aborigines (3,37). But in one study, the aborigines consumed 50,700 mg daily (37). In most cases, 210 mg is the appropriate amount. During pregnancy and nursing, kava should not be taken (4). Through additive effects, kava may enhance the effects of benzodiazepines, alcohol, and other sedative-hypnotic substances (4,38). It is recommended that patients on benzodiazepines avoid kava.

**Ginkgo**

Originally from East Asia, ginkgo trees (Ginkgo biloba) are now grown for their aesthetic value in North America and Europe. Ginkgo has been used for over 2,000 years in China as a tea to cure asthma. Today, it is the most popular herbal product in Germany and ranks among the top three herbal supplements in the U.S., where it is primarily used to prevent or treat memory issues (1, 3). Following a JAMA report on a clinical trial evaluating kava's usage for dementia patients, U.S. sales significantly climbed (39). The active ingredients, flavone glycosides (24 percent) and terpenoids (six percent), are often found in standardized commercial preparations. EGB 761 and LI 1370 are the extracts that are most frequently utilized in medicine (3) More than 40 controlled trials of ginkgo were reviewed by Kleijnen and Knipschild (40), and all but one of them reported clinically significant improvements in symptoms like memory loss, difficulty concentrating, weariness, anxiety, and depression. Nonstandard outcome measures were employed in the majority of the studies, which also had small sample sizes and poorly characterized patient groups. More recently, EGb 761 extract was employed at a dose of 120 mg daily in a 52-week, randomized, double-blind, placebo-controlled, multicenter study of over 300 patients with vascular dementia or Alzheimer's disease (39). On two of the three standardized rating scales, the group consuming ginkgo extract showed a much lower drop. An improvement of 4 points or more on the cognitive subscale of the Alzheimer's Disease Assessment Scale (41), or approximately a six-month reversal of symptoms, was the outcome measure. According to this metric, 27% of the EGb group showed improvement, but just 14% of the placebo group did. Despite being minor, these effects are similar to those found in cholinesterase inhibitor studies and could be

helpful to patients and their families. To determine which patients might benefit from this medication, further research is clearly needed. Numerous compounds identified in ginkgo extracts have been shown to have a range of pharmacological actions (3, 40). The ginkgolides, particularly ginkgolide B, block platelet-activating factor, and the flavonoids in ginkgo are believed to be antioxidants. Additionally, ginkgo extracts have been shown to enhance vascular perfusion through the modulation of arterial wall tone. Although ginkgo side effects are not common, they can include headache, upset stomach, and allergic skin responses (40). Preparations made from ginkgo have infrequently been linked to cerebral hemorrhage (42). Ginkgo's safety during nursing or pregnancy has not been proven. Extracts from ginkgo may interact with antithrombolytic and platelet-antiaggregating treatments because ginkgolide B is a strong inhibitor of platelet-activating factor (4,42). Additionally, patients with alcohol consumption or other hemorrhagic stroke risk factors should utilize them cautiously (42).

**Valerian**

The number of valerian species is about 250. The perennial Valeriana officinalis, which is indigenous to Europe and Asia, is the one that is most frequently used medicinally. Adding 3 to 5 grams of dried valerian root to hot water and filtering after 10 to 15 minutes is a common method for making valerian root tea (4). Furthermore, numerous tinctures and extracts have been made, with the aqueous and ethanol extracts differing significantly in content (3). The preparations that are accessible in the United States are frequently concoctions that contain additional substances, like passionflower. Several research studies have been undertaken to determine the effects of valerian extracts on sleep. 400 to 900 mg of valerian extract improved subjective sleep quality and reduced nocturnal awakenings and sleep latency in healthy human participants (43,44,45). Nevertheless, some trials showed noticeable placebo effects, and in other cases, the positive benefits of valerian were not observed until two to four weeks into the course of treatment. There are around 100 distinct components in valerian extracts. Since the entire valerian extract has been shown to have central nervous system activities not attributed to valeric acids, valepotriates, or volatile oils (3), it is uncertain which of them is primarily responsible for the pharmacological actions. The sedative and anticonvulsant properties of valerenic acids have been shown in laboratory animals, and valerian extracts have been shown to have a range of actions on GABA-ergic neurons, including decreased GABA breakdown, increased GABA release, and decreased GABA reuptake (3) Although they are uncommon, valerian preparation side effects can include mydriasis, headaches, contact allergies, gastrointestinal distress, and restless sleep (4). The main side effect of valerian is central nervous system depression (47), yet it seems to be reasonably safe in overdose (46). Regarding its safety during pregnancy and lactation, not much is currently known. Other sedative-hypnotics are the main drugs with which valerian interacts. Other central nervous system depressants may have their effects amplified by valerian's sedative properties.

**Other herbal hypnotics**

People have been drinking herbal teas for a long time because of their alleged sedative-hypnotic properties. Although many other herbs have previously been utilized, hops, lemon balm, chamomile, and passion flower are frequently used in these teas in addition to valerian (3). Of them, chamomile has been examined the most. Despite its widespread usage as a folk treatment (3,6), chamomile's efficacy as a sleep aid does not seem to have been experimentally confirmed.

Nonetheless, chamomile extract components have been shown to bind to GABA receptors in receptor-binding tests (6). The efficacy of the other herbs is much less well understood.

**A note of caution**

There are significant regulatory differences between the herbal remedies discussed here and prescription drugs. The Dietary Supplement Health and Education Act of 1994 governs herbal products as dietary supplements in the United States (5). In Germany, where herbal remedies are regulated more like medications, this is quite a different situation (3,5). Because of this, the majority of American psychiatrists find it challenging to obtain information regarding herbal remedies because there aren't many controlled studies of their safety and effectiveness published in English-language journals. Furthermore, the safety and effectiveness of these molecules are far less well understood than those of traditional drugs. The less stringent U.S. regulation also has the significant consequence of not standardizing herbal preparations in the same manner as pharmaceutical medicines. Variation in the raw plant material due to genetic (varietal) variables, climate, growth season, soil, rainfall, and other growing conditions, as well as the preparation method and the kind of solvent employed in the extraction process, can result in a wide range of product compositions (3). Therefore, an alcohol extract and tea made from dried herbs will have different compositions, as will a volatile oil extracted from the raw plant material. It is challenging to standardize preparations since these herbal remedies contain a variety of chemicals, and the active components are frequently unknown. Standardization of preparations is challenging. Additionally, if the plant material is costly, adulteration and substitution may take place. For all of these reasons, we cannot deduce, for example, that a U.S. product that is marketed as containing a particular percentage of ginkgo extract would be the same as a product such as EGb 761 created in Germany, where standardization is more rigorous (5). As a result, it is very challenging to extrapolate the findings of European research employing well-standardized preparations to the outcomes that could be achieved with American preparations bought from a pharmacy, health food store, or supermarket. When researchers attempt to assess the safety and effectiveness of these products, this challenge becomes much more problematic. A Los Angeles Times investigation that sent samples of 10 different brands of St. John's wort to an independent laboratory for analysis serves as an example of this issue (48). Half of the brands contained less than 80 percent of the labeled amount, and two brands contained more than 120 percent of the labeled amount. The amount of hypericin, a component that is frequently used for standardization purposes (3), ranged from 20 to 140 percent of the amount claimed on the label. Therefore, even if the labels suggest that the results are comparable, it is not possible to extrapolate late from the results of one preparation to those that may be anticipated with a different preparation.

## CONCLUSIONS

It is becoming more and more crucial for doctors to understand the herbal therapies that are frequently utilized by the patient groups they treat. Our patients will understandably expect their doctors to be able to respond to their inquiries on the uses, dangers, interactions, and adverse effects of herbal products, as they are sometimes exposed to dubious information about these items through the media or advertising efforts. Further, more and more patients are expressing a preference for solutions they consider to be "natural," and doctors who are knowledgeable about the available research will be in a better position to decide

whether it is safe and appropriate to suggest herbal remedies in certain situations. Even though there is mounting evidence that some herbal preparations are effective in treating mental health issues, the chemical complexity of the products and the lack of standardization of widely accessible preparations, in addition to the dearth of well-controlled safety and efficacy studies, make it difficult to translate the findings of efficacy studies into effective treatments for patients. Specifically, there aren't many well-controlled trials that contrast herbal therapies with prescription drugs. Psychiatrists should therefore refrain from recommending herbal medicines over well-established conventional medications just yet.

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