Phytomedicines for Prevention and Treatment of Mental Health Disorders

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KEYWORDS

• Herbal • Adaptogens • *Rhodiola rosea* • Maca • Nootropics • Fatigue • Anxiety • Cognitive function

KEY POINTS

- Many herb-drug interactions (HDIs) reported in preclinical, in vitro, and animal trials did not occur in human studies.
- Ginseng augments the activating effects of other agents, improving alertness, mental focus, energy, and cognitive function.
- In stable patients with schizophrenia, American ginseng (*Panax quinquefolius*) may improve verbal memory and reduce medication-related extrapyramidal symptoms.
- Balanced combinations of nootropics, herbs, and nutrients can improve anxiety, depression, memory, cognitive function and sexual function more than monotherapies.

INTRODUCTION

Phytomedicinal (herbal) compounds have a myriad of biological actions relevant to psychiatry: synthesis of neurotransmitters and their metabolizing enzymes, binding to neurotransmitters and receptors, membrane transport, stimulation or inhibition of central nervous system (CNS) activities, modulation of neuroendocrine systems, neuroprotection, enhancement of mitochondrial energy production, cellular repair, regulation of gene expression, and neurogenesis.[1,2]

The effects of most herbal medicines cannot be determined by analyzing individual constituents or by in vitro studies. In their excellent review, Sarris and colleagues[3] note that whole plant extracts can contain many bioactive compounds with synergistic and/or polyvalent effects. Synergy occurs when the sum of compounds exerting one main biologic effect is greater than their individual effects. Polyvalence refers to multiple biologic actions contributing to an overall effect when

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constituents have various physiologic effects or when one constituent has multiple effects. In addition, one constituent may affect absorption, distribution, metabolism, or excretion of other components. Furthermore, biochemical actions observed in vitro do not necessarily occur when herbs are consumed, digested, and metabolized in living organisms.

Purity and quality varies among products because of differences in root stock, soil, climate, harvest time, adulterants, and methods of extraction and drying. Resources that help identify high-quality brands[4] are available through the American Botanical Council (herbalgram.org) and fda.gov/medwatch, supplementwatch.com, ConsumerLab.com, and Drugs.com.

The selection of medicinal herbs for this article was based on credible clinical evidence of safety and efficacy, known biochemical mechanisms of action, usefulness in psychiatric practice, and the clinical experience of the authors. For research, phytochemistry, and genomics of *Rhodiola rosea, Eleutherococcus senticosus*, and *Schizandra chinensis*, see the article by Panossian; for *Ginkgo biloba*, the article by Diamond; for *St. John's wort*, the article by Sarris; and for *saffron, passion flower, valerian*, and *sage*, see the article by Ackhondzadeh in this issue.

HERB-DRUG INTERACTIONS

HDIs may enhance or interfere with therapeutic effects. Few herbs relevant to psychiatric practice have clinically significant medication interactions. Understanding the basic principles for evaluating herbs enables clinicians to safely use herbs to complement standard treatments while minimizing the risks of adverse events.

Pharmacokinetic and Pharmacodynamic Interactions

Pharmacokinetic interactions that affect medication serum levels most commonly include the induction or inhibition of cytochrome P450 (CYP450) isozymes and permeability glycoproteins (P-gp). Pharmacodynamic interactions involve risks of CNS side effects, hepatotoxicity, or bleeding. Additive effects can occur when an herb and a drug have similar effects, for example, if both are sedating, such that even though there are no pharmacodynamic interactions, the combination may cause excess sedation. Kennedy and Seely[5] reviewed studies of whole herb extracts from 21 herbs with evidence of HDIs in humans. Studies of single constituents were excluded because the concentration of an isolated constituent greatly exceeds that of the whole herb extract. The reviewers concluded that for most herbs with evidence of drug interactions in preclinical studies the effect on medication serum levels in humans is small and of no clinical significance. However, caution is required when combining herbs that interact with drugs having a narrow therapeutic window (a small difference between therapeutic and toxic levels or between therapeutic and subtherapeutic levels) and serious adverse effects outside the therapeutic range, for example, warfarin or digoxin. In addition, little clinical evidence exists regarding interactions of herbs with many anesthetics and antidepressants.

Minimizing Risks

The risks of HDIs can be minimized by monitoring for side effects and obtaining serum levels of medications that have a narrow therapeutic window. The vast majority of the alterations in drug levels involving herbs covered in this volume do not reach a level of clinical significance. Among herbs used in psychiatric practice, St. John's wort (*Hypericum perforatum*) has the greatest number of studies and reports showing interactions

with drugs. See the discussion of *St. John's wort HDIs* in the article by *Sarris* in this issue and the review by Zhou and Lai.[6]

Herbal effects on CYP P450 isoenzymes in vitro and in many animal studies are often not found to occur in human studies. Oral ingestion, digestion, and metabolism alter bioactive compounds such that they may have no effect or even the opposite effect observed in vitro. Some constituents cancel the effects of others. In addition, the impact of a botanical extract on P450 metabolism of one drug does not necessarily generalize to other drugs metabolized by the same isoenzyme because herbs and drugs compete for binding to an isoenzyme. Different drugs have different affinities for an isoenzyme that may be stronger or weaker than the affinity of the herb.

Evidence of effects on three P-gp substrates (saquinavir, metronidazole, and talinolol) is available for *G. biloba*. Although digoxin is also a P-gp substrate, there is no evidence that the herbs discussed in this article affect digoxin levels.[5] Nevertheless, the authors advise measurement of digoxin levels after initiating or changing the dose of any herbal preparation known to induce P-gp. Certain herbs, particularly *Panax ginseng*, American ginseng, and *E. senticosus* produce false-positive results of modest interference with serum digoxin levels. This occurs because they can directly affect certain digoxin assays using fluorescence polarization immunoassay. However, ginsengs and Eleuthero do not interfere with enzyme-linked chemiluminescent, immunosorbent, and turbidimetric digoxin assays.[7]

Most HDI studies include only healthy subjects. Izzo and Ernst[8] reviewed 128 case reports and 80 clinical trials of HDIs for 7 herbs, including ginkgo, Asian ginseng, kava, and St. John's wort. Yap and colleagues[9] reviewed HDIs for anticancer drugs. *Herbal Contraindications and Drug Interactions* by Brinker[10] is a well-documented resource. Other compendia of natural treatments are useful for general information but often present data from poorly documented, inconclusive cases without adequate qualifications. Therefore, readers are advised to check individual citations on HDIs before drawing conclusions.

HERBAL MEDICINES FOR ANXIETY AND INSOMNIA

Two systematic reviews found evidence for herbal supplements containing chamomile (*Matricaria recutita)* or kava (*Piper methysticum*) in the treatment of anxiety.[3,11] Anxiolytic phytomedicines usually work via gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the brain. Increasing GABAergic action reduces CNS stimulation and amygdalar overactivity (as occurs in anxiety disorders) (see the article by *Muench* in this issue).

Chamomile (M. recutita)

Although chamomile is widely used for anxiety and insomnia, research on this herb is limited. In a study of rat brain homogenates, chamomile extracts significantly inhibited GABA-metabolizing enzymes.[12] One component of chamomile, apigenin, has high affinity for benzodiazepine GABA receptors, modulates monoamine neurotransmission, and has neuroendocrine activity but causes minimal sedation. An 8-week randomized controlled trial (RCT) of moderately anxious patients with generalized anxiety disorder found that chamomile extract (220–1100 mg/d) significantly improved Hamilton Anxiety scores versus placebo.[13] Because the effects are mild, it is often necessary to combine chamomile with other sedative or anxiolytic herbs. Although generally low in side effects, as a member of the ragweed family, it can trigger allergic reactions.

Kava (P. methysticum)

Kava extract, a traditional ceremonial drink in South Pacific islands, contains active constituents, alpha-pyrones (kavalactones). Its actions include increased GABA transmission, blocking of lipid membrane sodium and calcium channels, monoamine oxidase B inhibition, and noradrenalin and dopamine reuptake inhibition. Kava has modest benefits in short-term studies of mild anxiety. Seven double-blind randomized placebo-controlled (DBRPC) studies (total $n = 380$) indicate significant improvement in HAMA scores with kava versus placebo.[14] Effect sizes were small, and only minor side effects were reported. Common side effects include gastrointestinal effect, allergic reactions, fatigue, headache, and light sensitivity; less common are restlessness, drowsiness, and tremor. Long-term heavy usage can lead to facial swelling, scaly rash, dyspnea, low albumin levels, increased gamma-glutamyl transferase (GGT) levels, decreased white blood cell and platelet counts, hematuria, and pulmonary hypertension.[15]

Case reports of kava hepatotoxicity, including 11 possible cases of liver failure, led to US Food and Drug Administration (FDA) warnings of potential liver injury.[16] Investigations implicate the use of incorrect plant parts or species, acetonic or ethanolic extraction, and inadequate storage resulting in hepatotoxic mold.[17] Ingestion of kava with alcohol, sedatives, or muscle relaxants can induce coma. In vitro studies found that kava extract and kava lactones inhibit P450 isoenzymes, CYP3A4, CYP2D6, and others involved in the metabolism of pharmaceuticals.[18] Sarris and colleagues[3] concluded that evidence supports the use of kava for anxiety but that safety issues need to be addressed. They recommend using only products from peeled roots of noble cultivars (species traditionally considered safe and therapeutic). Individuals with hepatic insufficiency should avoid kava. Monitoring liver functions in long-term users should be considered. There is no evidence to date regarding safety in children. Weighing mild benefits against risks of intoxication, abuse, dependency, medication interactions, and rare severe adverse reactions, the authors do not recommend kava until more information on safety, efficacy, quality, and reliable batch testing is available.

Theanine (Camellia sinensis)

Theanine is an amino acid found in *C. sinensis*, the herb in green tea, used for centuries for calming and medicinal effects. About 3 to 4 cups of green tea contain 60 to 160 mg of theanine. RCTs show some evidence of a mild relaxing effect, possible by inhibition of cortical excitation.[19,20] Theanine also has antioxidant and antiproliferative activities. In clinical practice, the authors use decaffeinated green tea for mild to moderate anxiety, particularly in patients who are sensitive to side effects from stronger agents. It has minimal and usually no side effects when started at 200 mg 1 to 3 times a day and titrated up to a maximum of 6 times a day. High doses can cause overactivation in patients with brain damage.

HERBAL ADAPTOGENS FOR ENERGY, MENTAL FOCUS, COGNITIVE ENHANCEMENT, AND SEXUAL FUNCTION

Herbal adaptogens contain hundreds of bioactive compounds, including metabolic regulators, and have demonstrated abilities to protect living organisms from damage caused by oxidative stress, toxic chemicals, infection, neoplasm, heat, cold, radiation, hypoxia, physical exertion, and psychological stress. See the article in this issue by *Panossian* for an in-depth discussion of research and mechanisms of action for important adaptogens, *R. rosea, E. senticosus*, and *S. chinensis*.

Korean or Asian Ginseng (Panax ginseng), American Ginseng (Panax Quinquefolius)

Ginsengs contain numerous bioactive compounds, particularly ginsenocides or ginseng saponins. *P. ginseng* increases nitric oxide production in endothelial cells, which is essential for blood flow and oxygen delivery. In a DBRPC 8-week study of healthy volunteers (older than 40 years) those given 400 mg/d ginseng had significantly better abstract thinking and reaction time compared with placebo. In a DBRPC crossover study of 32 healthy adults aged 18 to 40 years, 100 mg of *P. ginseng* significantly improved reaction time, accuracy, calmness, and working memory.[21] Average doses range between 300 and 800 mg/d. Side effects include over stimulation, anxiety, insomnia, tachycardia, gastrointestinal disturbance, headache, and reduced platelet aggregation. Use of anticoagulants is a contraindication.

American ginseng (*P. quinquefolius*) is less activating than Asian ginseng. In a 4-week DBRPC study of 64 stable patients with schizophrenia, those given American ginseng (preparation HT100) showed significant improvements in verbal memory and reduction in extrapyramidal symptoms compared with those given placebo.[22] In practice, ginsengs augment the activating effects of other agents, improving alertness, mental focus, energy, and cognitive function. American ginseng can reduce the anticoagulant effects of warfarin. In treating cognitive dysfunction due to stroke, trauma, or vascular disease, the authors get better results by combining *P. ginseng, P. quinquefolius*, and *E. senticosus*.

Maca (Lepidium Myenii)

Maca, a Peruvian herb that grows at high altitudes in the Andes, is used to enhance sexual function, fertility, energy, alertness, mental focus, mood, and physical resilience. Research on maca consists primarily of animal studies and a small number of methodologically limited human trials. For a review of published and unpublished studies see Gonzales.[23] Although studies suggested improvements in sexual desire and function, maca did not increase serum testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, or estradiol in men. In animal studies, the black variety of maca had positive effects on learning and memory, as well as decreasing acetylcholinesterase (AChE) levels in ovariectomized mice. In vitro studies found that maca reduced human brain malondialdehyde levels (marker of oxidative stress). A DBRPC pilot study found that maca (3.0 g/d) significantly reduced selective serotonin reuptake inhibitor–induced sexual dysfunction.[24] Toxic effects have not been reported in animal or human studies using herb that has been boiled before consumption. Animal studies found no teratogenic or carcinogenic effects. A population study comparing Peruvians living at high altitude who regularly consumed maca (starting with maca juices in childhood) with those living at lower altitudes who did not consume maca found that the maca users had better overall health and lower systolic blood pressure, body mass index, and rate of bone fractures. In recommended doses, maca causes minimal side effects; excess doses may cause overactivation. In clinical practice, the authors find that maca can be a useful adjunctive treatment for neural fatigue, sexual dysfunction, and infertility.

Arctic Root (R. rosea)—Clinical Guidelines

R. rosea can be beneficial in many conditions: fatigue from any cause; cognitive dysfunction; memory problems; depression; stress-related conditions; sexual dysfunction; weakness; infection; and cancer.[4,25] See article by *Panossian* in this issue for research review and mechanisms of action. When given alone or in combination with other adaptogens, it can enhance physical and intellectual performance,

attention, and memory. *R. rosea* absorbs best when taken on an empty stomach 20 minutes before breakfast and 20 minutes before lunch. Capsules may contain 100 to 180 mg dry root extract. The usual starting dose is 1 capsule before breakfast, increasing by 1 capsule every 3 to 7 days as needed. For patients who are sensitive to stimulants, prone to anxiety, elderly, or medically ill, starting with a fraction of a capsule reduces the risk of overstimulation. It is possible to open a capsule, dissolve the contents in juice or tea, store in an 8-ounce refrigerated container and titrate smaller amounts gradually. The average adult doses range is 150 to 600 mg/d, although some people respond to 25 mg/d.

As with other adaptogens, *R. rosea* may be taken before and during a stressful period or continuously long-term for chronic conditions. In some cases, the beneficial effects may fade after a few weeks or months. If this occurs, the dose could be increased, if necessary, up to a maximum tolerable dose (600–900 mg/d). Should this fail to restore efficacy, then "holidays"—discontinuation for 1 to 3 weeks at a time—may be indicated. Patients usually report improved energy during the first week on adequate doses. If this does not occur, or if efficacy fades, it is important to check the *R. rosea* brand to be certain it is of high quality.

Side effects

R. rosea is considered to be safe; adverse effects are rare. In some cases of individual sensitivity, anxiety, irritability, insomnia, headache, and rarely palpitations may occur. *R. rosea* stimulative effects can exacerbate agitation and irritability in bipolar disorder, although it can ameliorate depressive episodes in patients taking mood stabilizers. During the first 2 weeks, some patients report vivid dreams but not nightmares. If taken in the late afternoon or evening, stimulative effects can disturb sleep. Some individuals report increased libido and occasionally hypersexuality. Unlike amphetamines, *R. rosea* does not cause addiction or withdrawal symptoms. The onset of action is gradual and lasts 4 to 6 hours. At doses more than 600 mg/d, *R. rosea* can reduce platelet aggregation, resulting in increased bruising in some patients. No cases of bleeding have been attributed to *R. rosea*. It is advisable to monitor and adjust doses of anticoagulant medication and to discontinue aspirin and other substances that could affect bleeding. The herb should be discontinued 1 week before surgery. Although *R. rosea* showed in vitro inhibitory effects on CYP isoenzymes, in vivo rat studies found no significant effects on CYP450 metabolism of theophylline or warfarin or on anticoagulant activity of warfarin.[26]

In clinical practice, *R. rosea* can reduce menopause-related symptoms of fatigue, impaired cognitive function and memory, depression, and loss of libido. Anecdotally, in menopausal women who are amenorrheic for less than 12 months, resumption of menses while taking this adaptogen has been observed occasionally. Animal studies suggest that *R. rosea* binds to estrogen receptors but does not activate them.[4] In vitro *R. rosea* did not increase proliferation of human breast cancer cells.[4]

S. chinensis—Clinical Guidelines

S. chinensis is useful as an adjunctive treatment for sluggish depression, chronic fatigue, and fibromyalgia. It has been studied in combination with *R. rosea* and *E. senticosus* (see review by Panossian).[27] In vitro *S. chinensis* inhibited CYP3A4 enzymes. Paradoxically, in vivo animal studies showed it induces the same isozymes. In animal models, schisandra reduced warfarin levels, but this has not been demonstrated in humans. Until more is known, international normalized ratio (INR) should be monitored in patients on anticoagulants who are given schisandra.[28]

HERBAL COGNITIVE ENHANCERS

Herbal cognitive enhancers, called nootropics, have been widely used in Europe and Asia for centuries, yet they are virtually unknown to most American physicians. Generally low in side effects, nootropics have shown significant benefits in the treatment of cerebral ischemia, stroke, vascular dementia, hypoxic ischemia due to birth trauma, traumatic brain injury, age-related memory decline, and schizophrenia.[4]

Vinpocetine (Vinca minor)

Derived from periwinkle (*Vinca minor*) leaves, vinpocetine, a cerebral vasodilator, inhibits Ca^{2+}calcium/calmodulin-dependent cyclic guanosine monophosphate (cGMP) phosphodiesterase and increases intracellular cGMP in cerebral vascular smooth muscle, leading to decreased resistance, vasodilation, and increased flow in cerebral blood vessels. It also inhibits platelet aggregation and increases erythrocyte deformability, reducing blood viscosity and further enhancing blood flow.[28,29] Cerebral vasodilation, antioxidant, and antiinflammatory activities support the use of vinpocetine for ischemic stroke and other brain injuries. Most clinical studies of vinpocetine used small samples and short durations, limiting the conclusions that can be drawn. A photon emission tomographic (PET) study showed improved cerebral glucose kinetics and blood flow in peristroke areas.[30] In a 1-year study of 61 children with hypoxic ischemic encephalopathy from intracranial birth trauma, vinpocetine reduced seizure frequency, intracranial hypertension, and psychomotor sequelae.[31]

Vinpocetine has been shown to be safe, even in infants and the elderly, with only mild side effects of indigestion, nausea, headache, drowsiness, facial flushing, insomnia, headache, and dry mouth. Agranulocytosis was reported rarely. By selectively increasing cerebral, but not peripheral blood flow, vinpocetine is less likely to cause hypotension than other vasodilators, and it can be helpful in patients with magnetic resonance imaging, single-photon emission computed tomography, or PET scan evidence of blood flow abnormality.

Galantamine—Snowdrop (Galanthus nivalis)

In folk medicines of Russia and Europe, extract of snowdrop (*G. nivalis*) was used to prevent age-related memory decline. Galantamine (Razadyne), FDA approved for treatment of Alzheimer disease (AD), is a synthetic copy of 1 component of snowdrop. It is an allosteric modulator of nicotinic receptors and a weak inhibitor of AChE.[32,33] In an open trial, 280 patients with AD from the Swedish Alzheimer Treatment Study were given galantamine starting with 8 mg/d and gradually increasing to 24 mg/d as tolerated. After 3 years, rather than the expected decline, subjects had mean increases of 2.6 points on Mini Mental Status Examination (MMSE) and 5.6 points in Alzheimer Disease Assessment Scale-cognitive subscale.[34] For patients who do not tolerate gastrointestinal side effects of prescription galantamine, *G. nivalis* combined with *R. rosea* can be as effective and more tolerable.

Huperzine-A (Huperzia serrata)

Huperzine-A, an alkaloid derived from Chinese club moss (*H. serrata*) is a strong, selective, reversible AChE inhibitor with neuroprotective properties, including protection against free radicals, amyloid-β protein formation, glutamate, and ischemia.[35] It protects mitochondria, reduces oxidative stress, and upregulates nerve growth factor. Huperzine-A is rapidly absorbed, readily penetrates the blood-brain barrier, and has a long duration of AChE inhibitory action. In animal and primate studies, it

improves learning and memory.[35,36] Three double-blind trials with more than 450 people and 1 open trial done in China showed significant benefits in AD. In a DBRPC study of 78 patients with mild to moderate vascular dementia, those given Huperzine-A, 0.1 mg twice a day, significantly improved in scores on the MMSE, clinical dementia rating, and activities of daily living (ADL) after 12 weeks ($P<.01$), with no significant adverse events.[37] A 16-week DBRPC study of 210 individuals with mild to moderate AD reported cognitive enhancement only at doses more than 0.4 mg/d at week 16.[38] Other trials showed positive outcomes in vascular dementia, traumatic brain injury, age-related memory decline, and schizophrenia.[39,40] Huperzine-A is well tolerated with few side effects and minimal peripheral cholinergic effects.

Centrophenoxine (Meclofenoxate, Lucidril)

Centrophenoxine (CPH) is an ester of dimethyl-aminoethanol (DMAE), a component in choline synthesis, and *p*-chlorophenoxyacetic acid, a synthetic form of a plant growth hormone.[41] Elevation of brain acetyl choline is one mechanism for therapeutic effects in cerebral atrophy, dementia, and TBI. CPH also delivers DMAE rapidly to the brain where it is incorporated into nerve cell membranes as phosphatidyl-DMAE, an avid scavenger of OH-radicals.[42] In rat models of cerebral ischemia, CPH reduced cognitive deficits, suggesting a preventive role in cerebrovascular disease.[43] The administration of CPH (100 mg/kg body weight/d, intraperitoneal) to aged rats for 6 weeks resulted in increased activity of catalase, superoxide dismutase, glutathione reductase, and glutathione in brain tissues. Lipid peroxidation significantly decreased.[44]

In an 8-week DBRPC trial in patients with moderate dementia CPH showed increased psychomotor and behavioral performance in about 50% of subjects compared with 27% on placebo.[45] A 3-month DBRPC study of 62 geriatric patients with mild to moderate AD found that those given antagonic stress (a preparation of CPH, vitamins, and nutrients) showed significant improvements in memory, cognitive function, and behavior compared with those given nicergoline. Data suggest that nootropics work better when combined with vitamins, minerals, and other nootropics, such as piracetam.[46,47]

SUMMARY AND FUTURE DIRECTIONS

Phytomedicines contain bioactive compounds that can alleviate neuropsychiatric symptoms when used alone or in combination with other herbs, nutrients, and psychotropic medications. Evidence for the beneficial effects of herbal extracts on oxidative stress, mitochondrial energy production, cellular repair, neurotransmission, CNS activation or inhibition, neuroendocrine systems, and gene expression is expanding. Understanding the psychopharmacology and the potential clinical effects on anxiety, insomnia, cognitive function, and sexual function enables clinicians to evaluate the supplements being taken by patients and to advise them on safety and efficacy. Advances in testing constituents of herbal extracts continue to improve assessment of supplement quality. “Herbomics” is the use of proteomic, genomic, and other “omic” technologies to investigate the effects of herbs on gene regulation.[3] These and other modern technologies are improving the identification of specific herbal constituents, their mechanisms of action, and new therapeutic applications. Genetic studies will help evaluate the purity of rootstocks, develop more potent subspecies with greater specificity and diversity of therapeutic effects, and the accurately monitor the quality of products.

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