Herbal Adjuncts to Antidepressants

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Abstract

The intentional use of herbal medicines to increase efficacy or decrease adverse effects of antidepressant drugs is reviewed, with notes about situations (mostly isolated case studies) in which such combinations might have been harmful. *Hypericum perforatum* (St. John's wort), a common antidepressant herb, is reviewed first, given that there are a number of concerns about possible harms that might arise from its use with various antidepressants. Although a handful of case studies suggest that there are problems, there is little definitive information, and preclinical research suggests the possibility of benefits.

The safety of combining various herbs with monoamine oxidase-inhibiting drugs is reviewed next. Studies supporting the use of *Crocus sativus* (saffron) and *Ginkgo biloba* (ginkgo) to offset sexual adverse effects of selective serotonin reuptake inhibitors (SSRIs) are reviewed. *Pausinystalia yohimbe* (yohimbe) and its alkaloid yohimbine's ability to augment antidepressant therapy is discussed. The use of the herbal formula *Rikkunshi-tō* (*Liù Jūn Zǐ Wán*) to offset gastrointestinal adverse effects of SSRIs is reviewed. Finally, research on combining *Rauvolfia serpentina* (Indian snakeroot) and its alkaloid reserpine with antidepressants is mentioned. Much more research is needed in this area, given how frequently antidepressant drugs and herbs are used by patients.

Introduction

The current pharmaceutical approach to major depression includes a vast and growing array of agents (see Table 1, which includes definitions of abbreviations, some of which are used throughout this article). Unfortunately, for mild-to-moderately severe major depression, these drugs have been disappointingly ineffective for many people, according to a major meta-analysis.[1] For severe major depression, these drugs are quite effective. In addition there are troubling questions about higher doses of antidepressants, which consistently seem to increase the risk of self-harm and suicide in younger users.[2]

The current author has previously discussed at length herbal therapies for patients with depression who are not taking antidepressant drugs.[3,4] This article, instead, focuses on combining herbs with antidepressants, either to augment their efficacy or to decrease their toxicities. The herbs that are considered potential problems when combined with antidepressants are also discussed, and the overall lack of any solid substantiation for most negative herb–drug interactions is discussed. Most evidence supports that herbs can augment antidepressant drugs safely in patients who need them (see chart, Preclinical Evidence of Enhancement of Antidepressant Drugs with Herbs).

Hypericum

Hypericum perforatum (St. John's wort) remains the star among herbal antidepressants. There is no clear difference in efficacy between these drugs and St. John's wort extracts.[5] There is the most evidence that tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are most effective in primary care for mild-to-moderate major depression and not in severe depression. However, most of this research has not looked specifically at differences among these drugs and any natural treatment, let alone St. John's wort. St. John's wort and reversible monoamine oxidase inhibitors, selective (RIMOS) were significantly better-tolerated than all other categories of antidepressants in this meta-analysis. It has been argued convincingly—even taking into account the issues of concern regarding drug interactions with St. John's wort's constituent, hyperforin—that St. John's wort is ten times safer than existing prescription antidepressants.[6]

Hyperforin is an inducer of intestinal and hepatic CYP3A4 and intestinal P-glycoprotein; however, no approved antidepressant drug is a significant substrate for either of these catabolic pathways.[7] However, as there is some evidence that St. John's wort constituents may interfere with serotonin reuptake, and therefore, if it is taken with various antidepressants that also interfere with serotonin reuptake, patients could develop serotonin syndrome.

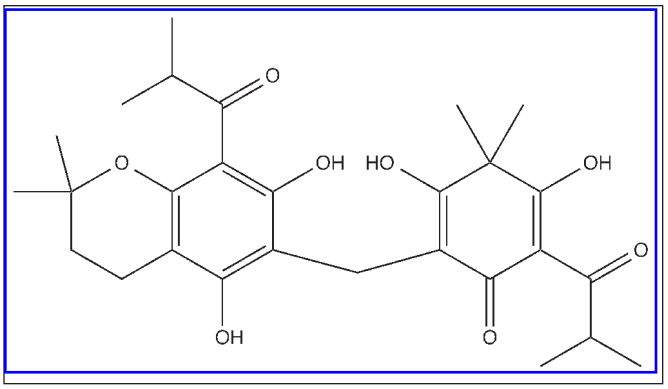

Figure 1. Chemical structure of uliginosin B.

A 28-year-old woman who had been taking fluoxetine for 1 year and St. John's wort extract for 1 month developed serotonin syndrome with seizures and rhabdomyolysis when she took eletriptan for an acute migraine.[8] Another case described serotonin syndrome in a 35-year-old woman taking fluoxetine, St. John's wort, and sumatriptan.[9] A 27-year-old woman experienced serotonin syndrome after combining the serotonin $5HT_{1A}$ receptor partial agonist buspirone with St. John's wort.[10]

SSRIs and tricyclic antidepressants (TCAs) are both associated with serotonin syndrome when taken by themselves, and case studies cannot establish if St. John's wort actually increases the risk of this outcome when coupled with these drugs.[11,12] Arguing against a strong increase in risk is an epidemiologic study that showed that a small number of adult Australians concurrently taking antidepressants and St. John's wort had no signs of serotonin syndrome.[13]

Another case described a 50-year-old woman who took St. John's wort and a single dose of paroxetine and became incoherent, weak, and slow without any signs or symptoms of serotonin syndrome.[14] She recovered completely without intervention. Details of an apparent case of an adverse interaction between venlafaxine and St. John's wort could not be obtained.[15]

A case report exists of a depressed patient who went into a manic episode when taking St. John's wort and sertraline at the same time.[16] Another woman with a mild traumatic brain injury and depression, who was taking fluoxetine and buspirone, became hypomanic with the addition of St. John's wort and *Ginkgo biloba* (ginkgo) leaf extract.[17] There are, however, cases of triggering mania with sertraline by itself.[18,19] St. John's wort can induce mania and is contraindicated in patients with bipolar disorder.[20,21] However, it is not clear if combining St. John's wort with SSRIs or any other drugs magnifies this effect significantly.

Various constituents from other members of the *Hypericum* genus have shown promise as adjuncts to antidepressant drugs in animal models. For example, uliginosin B (see Fig. 1) from *Hypericum polyanthemum* was studied in rats also receiving imipramine, bupropion, and fluoxetine, all (including the herbal compound) at subeffective doses.[22] These

Table 1. Categories of and Abbreviations for Major Antidepressant Drugs

Category	Mechanism(s) of action	Drugs in category
Reversible inhibitor of monoamine, oxidase selective (RIMOS)	Reversibly blocks monoamine oxidase (MAO)–A activity	Moclobemide, minaprine
Irreversible inhibitor of monoamine oxidase, non-selective (IIMON)	Irreversibly blocks MAO-A and B activity	Phenelzine, tranylcypromine, Isocarboxazid
Tricyclic antidepressant (TCA)	Blockage of presynaptic serotonin reuptake transporter (SERT), norepinephrine reuptake transporter, dopamine reuptake, muscarinic M2 receptor, adrenergic receptors, and histamine H1 receptor (to varying degrees)	Amitriptyline, imipramine, clomipramine, desipramine, doxepin, maprotiline
Selective serotonin reuptake inhibitor (SSRI)	Blockade of presynaptic serotonin reuptake transporter	Fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine
Serotonin-norepinephrine reuptake inhibitor (SNRI)	As SSRI, plus inhibits norepinephrine reuptake transporter	Venlaxafine
Serotonin antagonist and reuptake inhibitor (SARI)	SERT, norepinephrine, and dopamine transporter inhibitor, multiple serotonin receptor antagonist (but $5\text{-}HT_{1A}$ partial agonist)	Trazodone
Norepinephrine reuptake inhibitor (NRI)	Norepinephrine reuptake transporter inhibitor	Reboxetine, atomoxetine[a]
Noradrenergic and specific serotonergic antidepressant agents (NaSSA)	Presynaptic alpha-2 adrenergic receptor antagonist, indirect $5\text{-}HT_{1A}$ agonist (not reuptake inhibitors), $5\text{-}HT_{2A}$ antagonist	Mirtazapine,[a] mianserin[a]

[a]No reports of interactions of any kind between this drug and herbal products could be identified.

combinations were as effective for relieving depression as full doses of the drugs or the herbal compound in isolation. Low-dose crude extracts of *H. polyanthemum* were also effective when combined with subtherapeutic doses of antidepressants. The mechanisms of action of uliginosin B and *H. polyanthemum* were shown to involve monoaminergic neurotransmitters, but in ways that did not mimic that of any existing antidepressant.

There is no definitive evidence of any St. John's wort–antidepressant adverse drug interactions, but neither is there definitive evidence of benefits from combining them.[23] Controlled trials of low-dose St. John's wort augmentation in patients with depression that is not responding to conventional antidepressants should be undertaken to carefully determine if the drugs might be effective in combination with St. John's wort.

Monoamine Oxidase Inhibitors, Herbs, and Food

One of the earliest categories of antidepressants was comprised of irreversible inhibitors of monoamine oxidase, nonselective (IIMONs), which irreversibly blocked both monoamine oxidase (MAO)–A and –B activity. These were highly problematic, because MAO-A, the predominant form of the enzyme in the gut and liver, was also responsible for degrading tyramine and similar amines from foods that contain them. Combining tyramine-rich foods (mainly fermented foods) with IIMONs was a recipe for disaster, with very high levels of tyramine building up in monoamine storage granules in adrenergic neurons, leading to rapid release of norepinephrine and other catecholamines from the nerve terminal. A potentially fatal hypertensive crisis ensues in such a situation. IIMONs were almost abandoned because of this problem, but they were and are still quite effective for some patients, and so have been rehabilitated with careful training of patients regarding what foods and drugs to avoid taking simultaneously.

Stimulant herbs that increase norepinephrine levels, such as *Ephedra sinica* (*ma huang*) and *Pausinystalia yohimbe* (yohimbe), should not be taken with IIMONs.[24] It is also not wise to combine caffeine-containing herbs with IIMONs for the same reason. There is one case study of a *Panax ginseng* (Asian ginseng)–containing mixture that likely also contained caffeine (the full ingredients of the product were not disclosed, but this type of product was common at the time) causing hypertension in a patient who was taking the IIMON phenelzine, but this report is highly dubious and incomplete.[25]

Given the lack of any other reports of interactions between IIMONs and Asian ginseng before or since this one low-quality case report, the lack of a mechanism to explain the interaction, the low quality of this case study, and the high likelihood that caffeine was the actual problem, there is no reason to avoid Asian ginseng in patients taking IIMONs at this time.

Herbs containing high levels of L-3,4-dihydroxyphenylalanine (L-dopa) also need to be avoided, as MAO-A and -B are involved in degrading this compound and it can build up to high levels in patients taking IIMONs, resulting in hyperpyrexia, nausea, and vomiting, and even psychosis. *Mucuna pruriens* (velvet bean) is the main herb in relatively common use with high levels of L-dopa.[26] Some other legumes are also a problem in this regard, notably fava beans.

RIMOS do not interact with tyramine at usual clinical doses. The reversibility of RIMOS inhibition of MAO-A makes them safe. However, RIMOS can still be a problem with foods and herbs containing L-dopa, as L-dopa is degraded about equally by MAO-A and -B.

There are some herbs that act as RIMOS, notably the fairly potent herbs *Peganum harmala* (Syrian rue) and *Banisteriopsis caapi* (*ayahuasca*).[27,28] Both of these contain harmaline alkaloids that are largely responsible for this action. *Passiflora incarnata* (passionflower) contains only trace amounts of these alkaloids and is not a clinically significant RIMOS.[29] Syrian rue in particular is used on its own to treat depression.[30] There is a theoretical concern that combining MAO-inhibiting herbs such as these with MAO-inhibiting drugs of any kind could lead to synergistic toxicity. No reports of such interactions were recovered from the literature at this time, however.

Serotonin-Modulating Drug Adjuncts

One extremely common adverse effect of SSRIs is sexual dysfunction, mainly decreased libido but also erectile dysfunction and impairment of various physiologic aspects of female sexual function. Several herbal medicines have been assessed for their ability to offset adverse sexual effects of SSRIs, most recently *Crocus sativus* (saffron) stigmas. This well-known spice has already proven to be an effective antidepressant for patients with mild-to-moderate major depression by many mechanisms, some involving serotonin and many not related to serotonin.[31] These trials utilized crude hydroethanolic extracts of saffron.

In a double-blinded trial, 34 women taking fluoxetine for major depression and experiencing sexual dysfunction were randomized to add either 15 mg of saffron extract twice daily or placebo for 4 weeks.[32] There was significantly greater improvement in overall sexual function, arousal, and lubrication, and decreased pain with saffron compared to placebo, with no difference in adverse effects among the treatment groups.

A very similar double-blinded, randomized trial in 30 men with sexual dysfunction caused by fluoxetine showed that saffron, at a dose of 15 mg twice daily, was significantly more effective for improving erectile function, intercourse satisfaction, and overall sexual function (but not libido) scores than placebo.[33] Notably, there were no signs of ill effects of combining saffron and fluoxetine.

Ginkgo biloba (ginkgo) leaf extract has also been assessed for offsetting antidepressant-induced sexual dysfunction. Two early open trials suggested that ginkgo, standardized extracts at doses of 60–120 mg twice daily, could improve libido in patients taking SSRIs, TCAs, and monoamine oxidase inhibitors of various types.[34,35] One open trial could not confirm these results, but it used an uncharacterized product in the unusual

dose of 300 mg three times daily, suggesting that the product used was not the same as that used in the other open trials and possibly accounting for the lack of activity.[36]

The single randomized, double-blinded trial available compared the same standardized extract as the positive trials at doses escalating from 120 mg to 160 mg to 240 mg daily, over 8 weeks, to placebo in 37 men and women with sexual dysfunction who were taking SSRIs or nortriptyline, a TCA.[37] There was no difference in efficacy among the groups. A larger trial is still probably indicated to be certain about efficacy, but ginkgo should probably be reserved for situations in which nothing else has worked and there is little to lose, given the herb's safety. As a side note, ginkgo has no pharmacokinetic interaction with bupropion in humans.[38]

Pausinystalia yohimbe (yohimbe) bark contains alkaloids including yohimbine that act as presynaptic alpha-2 adrenergic receptor antagonists. These receptors act as reuptake portals for norepinephrine, so the inhibition has a central nervous system–stimulating effect, particularly on libido and mood.[39] Yohimbine is a well-researched and proven aphrodisiac that could be useful for offsetting sexual adverse effects of antidepressants, and that also has antidepressant effects. Thus it was not surprising that one single-blinded clinical trial showed that yohimbine, in a dose of 5–30 mg t.i.d., enhanced the efficacy of fluvoxamine in patients with resistant depression.[40]

In the most rigorous, double-blinded study to date, 5–10 mg of yohimbine t.i.d. significantly speeded the antidepressant response to fluoxetine in patients with major depression.[41] However, 5 of 24 patients who were randomized to fluoxetine plus yohimbine left the study because of a new onset of hypertension or urinary retention, both known adverse effects of yohimbine. In a clinical trial of women with SSRI-related sexual dysfunction, yohimbine was not effective, but neither were mirtazapine or olanzapine.[42]

Whole-plant yohimbe has not been formally studied but should be considered as an alternative as an adjunct to insufficient antidepressant therapy, particularly given the relative lack of availability of yohimbine. Typical doses of tincture (1:3 weight:volume ratio) are 2–5 drops t.i.d.

The Japanese herbal formula Rikkunshi-tō, is based on the original Chinese herbal formula *Liù Jūn Zǐ Wán* ("Six Gentlemen Tea Pills"), which originated in the *Tài píng huì mín hé jì jú fang* (Formulary of the Pharmacy Service for Benefiting the People in the Taiping Era) by the Imperial Medical Bureau from 1107 AD. This formula has a long history of use, supported by clinical trials, for improving digestive function.[43]

Rikkunshi-tō has a long history of use, supported by clinical trials, for improving digestive function.

The ingredients in the version of *Rikkunshi-tō* in granulation form (2.5 g t.i.d.) used in a study are listed in Table 2. SSRIs often cause digestive problems, and a randomized open trial was conducted to determine if the formula could offset dyspepsia caused by fluvoxamine in patients with major depression.[44] Nausea and overall adverse effects were significantly lower in the study's combination therapy group, compared to the study's fluvoxamine-only group. The antidepressant efficacy of the drug was not enhanced by the formula.

There are no reports on beneficial combinations of herbs with the serotonin antagonist and reuptake inhibitor (SARI), trazodone, the major SARI antidepressant in use. One convincing case study did report on an 80-year-old woman with moderate Alzheimer's disease who went into a coma after combining *Ginkgo biloba* extract and trazodone that was reversed instantly with administration of flumazenil, a gamma-aminobutyric acid (GABA) inhibitor.[45] Trazodone has no known effects involving GABA, while ginkgo is a mild GABA agonist, which does not cause coma in isolation, strongly implicating the combination of the two agents

Table 2. *Rikkunshi-tō (Liù Jūn Zǐ Wán)* Components

Herb & part used	Common names	Amount in formula
Panax ginseng root (often *Codonopsis* spp. is substituted)	Asian ginseng, *rén shēn* (codonopsis, *dǎng shēn*)	4 g (12 g if *Codonopsis*)
Atractylodes macrocephala rhizome	White atractylodes, *bái zhú*	4 g
Wolfiporia cocos sclerotium	Hoelen, *fú líng*	4 g
Glycyrrhiza uralensis prepared root	Asian licorice, *zhì gān cǎo*	1 g
Citrus reticulata aged peel	Tangerine, *chén pí*	2 g
Pinellia ternata prepared rhizome	Pinellia, *zhì bàn xià*	4 g
Zingiber officinale rhizome	Ginger, *gān jiāng*	0.5 g
Zizyphus jujube fruit	Jujube, *dà zǎo*	2 g

Preclinical Evidence of Enhancement of Antidepressant Drugs with Herbs

Herbal compound (source)	Drug(s)	Results	Reference
Curcumin, water-soluble form (*Curcuma longa*, turmeric)	Multiple	Subtherapeutic doses of multiple drugs effective when combined with curcumin product in mice	a
Berberine (*Berberis* spp., barberry, among others)	TCA, SSRI, IIMON, SNRI, bupropion	Subtherapeutic doses of multiple drugs effective when combined with berberine in mice	b
Hesperidin (citrus among many others)	SSRI	Subtherapeutic doses of fluoxetine effective when combined with low doses of hesperidin in mice	c
Ursolic acid (most plants)	Bupropion (but not SSRI, TCA)	Subtherapeutic doses of bupropion with low doses of ursolic acid effective in mice	d
Ursolic acid	SSRI, NRI	Subtherapeutic doses of fluoxetine and reboxetine with low-dose ursolic acid effective in mice	e

[a]Kulkarni SK, Akula KK, Deshpande J. Evaluation of antidepressant-like activity of novel water-soluble curcumin formulations and St. John's wort in behavioral paradigms of despair. Pharmacology 2012;89:83–90; [b]Kulkarni SK, Dhir A. Possible involvement of L-arginine-nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) signaling pathway in the antidepressant activity of berberine chloride. Eur J Pharmacol 2007;569:77–83; [c]Souza LC, de Gomes MG, Goes AT, et al. Evidence for the involvement of the serotonergic 5-HT(1A) receptors in the antidepressant-like effect caused by hesperidin in mice. Prog Neuropsychopharmacol Biol Psychiatry 2013;40:103–109; [d]Machado DG, Neis VB, Balen GO, et al. Antidepressant-like effect of ursolic acid isolated from *Rosmarinus officinalis* L in mice: Evidence for the involvement of the dopaminergic system. Pharmacol Biochem Behav 2012;103:204–211; [e]Colla AR, Oliveira A, Pazini FL, et al. Serotonergic and noradrenergic systems are implicated in the antidepressant-like effect of ursolic acid in mice. Pharmacol Biochem Behav 2014;124:108–116.

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; IIMON, irreversible inhibitor of monoamine oxidase, non-selective; SNRI, serotonin–norepinephrine reuptake inhibitor; NRI, norepinephrine reuptake inhibitor.

as the cause of her coma. Although no other reports have appeared in the literature about a problem with this combination, it should still be avoided as a precaution.

TCA Adjuncts

A clinical trial investigating a combination of 5–10 mg of yohimbine with desipramine did not find an improvement in mood in patients with severe depression that was refractory to other treatment.[46] However, yohimbine did prevent the tendency of desipramine to cause hypotension. A small double-blinded, placebo-controlled trial found that 4 mg of yohimbine t.i.d. also reduced orthostatic hypotension caused by clomipramine in depressed patients.[47] A dose of 4 mg of yohimbine also offset dry mouth caused by TCA without causing any adverse effects in a case series.[48]

Reserpine is an alkaloid found primarily in *Rauvolfia serpentina* (Indian snakeroot) and related species. It is well-known as an antihypertensive, but can potentially cause depression in excess doses or in sensitive patients because of reserpine's depletion of catecholamine storage granules. It is surprising then that it would even be considered for antidepressant augmentation research, but a study was conducted.

A small double-blinded, randomized trial had 7 patients with major depression that was nonresponsive to TCA added the enormous dose of 5 mg b.i.d. of reserpine (typically antihypertensive doses are 0.5 mg q.d.) or placebo for 2 days.[49] There was no clear benefit and 2 patients became hypomanic with this treatment. Overall, depression was not aggravated, although the duration of the study was so short that it is not clear what might have happened. Unfortunately, this study did not determine if more reasonable, low-dose reserpine, and particularly whole-root Indian snakeroot, would interact with antidepressants.

Conclusion

Given the wide use of antidepressant medications, the relative lack of research on their interactions with herbal products is surprising, particularly given how often herbal medicines are used by patients with depression.[50] Although some case studies have suggested specific potential adverse effects, these studies are few and far between, and often not definitive.

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There are several studies suggesting real potential to augment the efficacy of antidepressants and reduce their toxicities, indicating a need for more research. In the meantime, this article provided some practical guidance on beneficial combinations to consider and about the handful of problem combina-

tions that should be avoided until more information becomes available clarifying the situation.

Leaving patients to decide whether to combine herbs and antidepressant drugs without guidance, which they often do in an honest attempt to improve their situations and not out of a rejection of conventional medicine,[51] is not ideal, although this is commonplace. Ideally, clinicians should provide reasonable suggestions regarding potentially beneficial combinations and monitor them to provide patients with the best outcomes. ■

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