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Potential interactions of popular adaptogens (Withania somnifera, Rhodiola rosea) with psychotropic drugs

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Abstract

Purpose: The aim of this narrative review is to synthesize existing literature regarding the neuropharmacological effects and potential drug interactions of two of the most commonly used adaptogens: Withania somnifera (Ashwagandha), and Rhodiola rosea; as well as develop practical guidelines for the safe use of these supplements with psychotropic medications.

Methods: This narrative review examined all relevant clinical, observational, and mechanistic studies regarding Ashwagandha and Rhodiola that were identified through a search of PubMed, Cochrane and the ScienceDirect between 2013 and 2024. Data extracted from each study included data concerning stress-, and mood-related outcome measures, GABAergic and monoaminergic mechanism of action, and whether either herb interacts with cytochrome P450 enzymes. In addition, data were extracted regarding reported, or mechanistically likely, interactions with antidepressants, anxiolytics, hypnotics, and other psychotropic drugs.

Results: Ashwagandha has been consistently shown to have significant anxiolytic and stress reducing effects, and has a relatively favorable pharmacokinetic profile compared to many of its herbal counterparts. However, it has GABAergic activity which can lead to

pharmacodynamic interactions with benzodiazepines, z-drugs, and other central nervous system depressants. Rhodiola, on the other hand, has been shown to have activating and antidepressant-like effects, and has been found to modulate monoaminergic transmission, as well as inhibit the activity of cytochrome P450 enzymes CYP2D6 and CYP3A4. These findings suggest that Rhodiola may increase the risk of serotonin toxicity when combined with certain psychotropic medications, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, and potentially increase the plasma concentrations of co-administered psychotropics due to decreased metabolic clearance. For this reason, the majority of studies reviewed in this article were conducted in healthy individuals, and therefore, very few studies have evaluated the efficacy or safety of either Ashwagandha or Rhodiola in patients who are taking multiple medications concurrently for the treatment of psychiatric disorders.

Conclusions: Based on the findings of this review, both Ashwagandha and Rhodiola cannot be viewed as pharmacologically inert supplements that can be safely used in conjunction with prescription medications for the treatment of psychiatric disorders. Therefore, they should be carefully assessed prior to initiating therapy, with consideration of the individual's concurrent prescription medications and comorbid medical conditions. Furthermore, they should be initiated at low doses and monitored closely for symptoms of sedation, serotonergic effects, and signs of drug accumulation. Additionally, further research is needed to determine the long-term safety and efficacy of combining Ashwagandha or Rhodiola with various prescription medications, in order to establish their place within the broader context of psychiatric treatment options.

Keywords: withania, rhodiola, herb-drug interactions, psychotropic drugs, phytotherapy

1. Introduction

Stress exists as a natural human response that activates when people face dangerous or overwhelming circumstances. This reaction manifests as physical exhaustion and psychological symptoms such as irritability or anxiety. If persistent stress is not addressed, it can progress to

chronic stress or burnout, which represents an unmet medical need for intervention [1]. Nowadays, people show increasing interest in self-care practices and natural substances to build resistance against stress. Plant extracts known as adaptogens have become popular because they help individuals handle physical stress without increasing oxygen consumption [2]. Traditionally, natural adaptogens like Withania somnifera (ashwagandha) and Rhodiola rosea (golden root) were used to aid recovery from illness, combat weakness, and improve memory function [2]. Ashwagandha, also called Indian ginseng, has in recent times gained worldwide popularity due to its reputation as a powerful adaptogen [3]. In Ayurvedic medicine it has long been used as a "rasayana" (rejuvenator) for general well-being and in specific therapies [4]. Similarly, Rhodiola rosea is notable for being the main adaptogen approved by the HMPC/EMA for the indication of "stress," known to influence the release of stress hormones and enhance energy metabolism [1].

The widespread use of botanical products has raised serious concerns about potential herb-drug interactions (HDIs) [5]. Due to the multitude of active constituents in herbal preparations, HDIs are statistically much more likely to occur than drug-drug interactions [6]. Self-medication further complicates clinical practice, as many individuals using complementary and alternative medicine (CAM), including psychiatric patients, do not report this to their physicians [7]. Patients often believe that herbal remedies are "natural" and therefore safe, but in fact these products can significantly affect the pharmacokinetics of co-administered drugs by altering their absorption, distribution, metabolism, and excretion [6]. In recent years, retrospective analyses have documented adverse effects during the concomitant use of antidepressants with adaptogens (particularly Withania somnifera and Rhodiola rosea). These interactions appear to result mainly from pharmacokinetic interference, such as inhibition of cytochrome P450 enzymes and/or P-glycoprotein efflux, when herbs and antidepressants are taken together [8]. The aim of this review is to provide an overview of the pharmacokinetic interaction profiles of these two popular adaptogens as a basis for the safe clinical use of herb-drug combinations.

2. Mechanisms of Herb-Drug Interactions

Phytochemicals contained within the adaptogenic plants ashwagandha and rhodiola can affect various aspects of the body's ability to metabolize drugs including liver drug-metabolizing

enzymes. Phytochemicals found in these plants can inhibit components of the cytochrome P450 system, which includes isoenzymes CYP3A4 and CYP2D6 [5, 6]. Once the cytochrome P450 system is inhibited with respect to either CYP3A4 or CYP2D6, the rate at which drugs are metabolized is slowed down resulting in increased plasma levels of drugs and an increase in the risk for toxic side effects from the drug(s) [5, 6]. For example, extracts of Rhodiola rosea have been demonstrated to inhibit CYP2D6, and two flavonoids (rhodiosin and rhodionin) present in the extracts of Rhodiola rosea are potent non-competitive inhibitors of CYP2D6; therefore, the clearance of drugs that are substrates of CYP2D6 (e.g., some antidepressants or beta blockers) would be delayed [2, 5]. In addition, many commercially available preparations of R. rosea were demonstrated to inhibit CYP3A4 in vitro; therefore, a large number of medications that are substrates of CYP3A4 (e.g., benzodiazepines, antipsychotics, statins, etc.) could be affected by co-administration with R. rosea [2, 5, 6]. However, based on studies of the root of W. somnifera, there is no evidence of significant inhibition of CYP3A4 or CYP2D6 in vivo; therefore, it is likely that the risk of these specific metabolic interactions is low [3, 4]. While there appears to be little risk of elevating drug concentrations due to CYP inhibition based on these findings, the overall body of evidence is still limited [3, 6]. When an herb inhibits one of the major CYP enzymes, it may result in the accumulation of co-administered drugs; and this accumulation may result in exaggerated drug effects or adverse drug reactions (e.g., excessive sedation, hypotension, or cardiac toxicity) due to decreased clearance of drugs when enzyme inhibition occurs [5, 6, 8].

Rhodiola rosea: Rhodiolins and rosinin in R. rosea inhibit CYP2D6 non-competitively [2, 5]. Many R. rosea extracts also inhibit CYP3A4, which can lead to reduced rates of metabolic processing of psychotropic medications (e.g., certain SSRIs, antipsychotics) thereby increasing plasma levels of these medications [2, 5, 6].

Withania somnifera: Ashwagandha root has shown no statistically significant inhibition of CYP2D6 or CYP3A4 in humans in clinical studies [3, 4]. While there appears to be little risk of elevating drug concentrations due to CYP inhibition based on these findings, the overall body of evidence is still limited [3, 6].

Any herb that causes inhibition of CYP3A4 or CYP2D6 (or P-glycoprotein), will generally lengthen the half-life of a drug and can lead to drug accumulation and toxicities [5, 6]. For example, depressed CYP3A4 activity can lead to elevated benzodiazepine and/or mood-

stabilizing drug plasma concentrations, whereas depressed CYP2D6 activity can have an impact upon the metabolism of drugs that are metabolized by this enzyme. On the contrary, enzyme induction (most notably by some herbs such as Hypericum perforatum St. John's Wort), can decrease the plasma concentration of drugs and thus lead to inadequate therapy [5, 6, 7]. Healthcare providers should monitor patients who are receiving psychiatric medications and herbal remedies simultaneously, because even mild inhibition of enzymes can affect how drugs are processed pharmacokinetically and dose adjustments or timing modifications may need to be made to avoid adverse reactions [1, 6, 7].

Pharmacodynamic Interactions

Pharmacodynamic interactions occur between an herb and a drug when they interact at the same site within the body. One classic example of this is central nervous system (CNS) depression. CNS depressant herbs and CNS depressant drugs that work by inducing sedation can potentiate one another's effects. Examples of this interaction are when sedatives (benzodiazepines, certain antipsychotics) are taken with sedative herbs (valerian, kava, chamomile) to produce excessive drowsiness, decreased respiration, and decreased cognition [1, 6]. When an herb and a drug interact at inhibitory sites (i.e. GABA receptors), the potential for serious adverse reactions exists, including severe sedation and/or respiratory depression [6, 7]. Additionally, if an herb influences neurotransmitter systems, it may enhance the action of a drug. An example of this is the enhancement of serotonergic activity when an herb (St. John's Wort and Saffron) is used in conjunction with an SSRI or other serotonergic agent. The additive effects of the overlapping serotonergic activity may cause excessive elevation of serum levels of serotonin and can produce symptoms of serotonin syndrome (agitation, tachycardia, muscle stiffness) [1, 6, 8]. Other types of additive effects exist with herbs that cause decreased blood pressure or exhibit anticholinergic properties combined with drugs that possess the same properties can potentiate side effects (dizziness, urinary retention) [6, 8].

Increased Sedation: The concurrent administration of sedative herbs and CNS depressant drugs produces additive CNS depression (E.g. Valerian or Kava taken with benzodiazepines or certain anticonvulsants can produce significant sedation or respiratory compromise) [6, 7].

Synergy of Serotonin: Herbs that elevate the levels of serotonin (e.g. St. John's Wort, Tryptophan Supplements) in combination with drugs that also increase serotonin levels (serotonergic antidepressants) can produce an excessive serotonergic response [1, 6, 8].

Examples of Other Potential Pharmacodynamic Interactions: Any herb that works on the same

receptor system as a psychotropic medication can interact with the medication. For example, the addition of anticholinergic drugs with herbs that contain anticholinergic alkaloids (belladonna, scopolamine) may exacerbate the cognitive impairments produced by the anticholinergic drugs; similar to the effects of dopaminergic or adrenergic herbs that may interact with the dopamine or norepinephrine pathways of psychotropic drugs [6, 7].

To summarize, pharmacodynamic herb-drug interactions occur through additive or synergistic activities of the herb and the drug on the same biological process. Therefore, the final outcome of co-administration of an herb and a drug can either be increased efficacy or increased side effects. Healthcare professionals should be aware of these additive effects and provide counseling to their patients who are taking psychotropic medications about the potential for herb-induced potentiation of the effects of their medications, particularly concerning sedation and mood modulation [1, 6].

3. Withania somnifera (Ashwagandha)

Adaptogenic effects of ashwagandha

Ashwagandha has long been classified as an Ayurvedic “rasayana” plant, used to promote the body’s ability to adapt to stress and maintain equilibrium [2, 3]. As an adaptogen, ashwagandha is thought to influence the body’s response to stress and build endurance to both physical and emotional stresses. Research supports ashwagandha’s traditional use as an adaptogen: in several clinical trials, researchers reported that ashwagandha supplementation decreased serum cortisol levels; lowered subjective scores of stress and anxiety; and enhanced sleep quality and mood, thereby reducing feelings of stress and anxiety [3, 9, 10]. The anti-stress impacts of ashwagandha are considered to be the basis of its use in treating anxiety, fatigue and other conditions associated with stress.

Several key adaptive properties of ashwagandha are:

HPA-axis modulation: Modulating normal ranges of stress hormones (e.g., cortisol) to combat prolonged exposure to stress [3].

Improved mental endurance: Enhancing the general sense of well-being and reducing anxiety and fatigue during periods of stress [3].

Improved sleep: Enhancing quality of sleep and decreasing symptoms of insomnia. It is possible that the sleep-enhancing effects of ashwagandha result from its sedative effects [3].

Anti-oxidative and anti-inflammatory actions: Protecting cells from oxidative stress and inflammation caused by chronic stress [11, 15].

The overall adaptations of ashwagandha enable the body to return to homeostasis during times of stress. For instance, a recent meta-analysis of adaptogenic plants indicated that ashwagandha consistently lowered cortisol and Perceived Stress Scale (PSS) scores in adults experiencing stress [12, 13].

Mechanisms of Action

Ashwagandha's mechanisms are multi-faceted, affecting the nervous, endocrine and immune systems. Ashwagandha contains bioactive withanolides and related compounds in its root system, which bind to the body's neurotransmitter and hormonal pathways [11, 15]. One of the major mechanisms of ashwagandha appears to be an increase in inhibitory neurotransmission in the brain. Studies indicate that ashwagandha can increase GABAergic activity similar in type to a weak benzodiazepine. In animal studies, ashwagandha extracts have been demonstrated to increase GABA levels (the main neurotransmitter responsible for promoting calmness) and act as an agonist at the GABA_A receptor. The GABAergic impact of ashwagandha likely contributes to its anxiolytic and sedative properties. Additionally, ashwagandha may contribute to augmentation of serotonergic pathways, because increases in brain serotonin have been observed which can also decrease anxiety and improve mood [3].

Additional mechanisms that may be involved in the actions of ashwagandha include:

Regulation of HPA axis: Ashwagandha appears to inhibit overactive hypothalamic-pituitary-adrenal responses (reducing ACTH and cortisol secretion) during stress [3, 13].

Modulation of Neuroendocrine System: Ashwagandha has an effect on thyroid hormones and neurotrophic factors, providing support for energy and cognition during periods of stress [11].

Antioxidative/Neuroprotection: Through the reduction of oxidative stress and inflammation, ashwagandha may protect neurons from stress-induced damage and improve cognitive performance [11, 15].

In conclusion, the adaptogenic and calming effects of ashwagandha likely occur via multiple mechanisms including: suppression of stress hormones; enhancement of inhibitory neurotransmitters (specifically GABA); and protection of the brain from damage caused by chronic stress [3].

Interaction with Central Nervous System (CNS) Depressant Medications

While ashwagandha is typically safe to use alone, it has mild sedative/anxiolytic properties that can interact pharmacodynamically with other CNS depressants. The most common interaction concern is additive sedation. If ashwagandha is consumed simultaneously with sedatives and/or alcohol, their combined sedative effects may amplify drowsiness; interfere with coordination; and slow down cognitive and motor responses [6, 7]. The sedative interactions between ashwagandha and other CNS depressants are based on pharmacodynamics (i.e., effect-based) rather than pharmacokinetics (i.e., metabolic). Therefore, clinicians and consumers should exercise caution when using ashwagandha in conjunction with other CNS depressants [6, 10].

Some of the primary interaction concerns with ashwagandha include benzodiazepines (e.g., diazepam and alprazolam). Ashwagandha and benzodiazepines each enhance GABAergic inhibition in the brain. Using them in concert will increase the risk of excessive sedation and loss of motor coordination. Consumers may experience pronounced drowsiness; dizziness; slowness of reflexes; and increased likelihood of falls or accidents. Cognitive dullness (e.g., memory problems or slowness of thought) may also be exacerbated. Practically speaking, if a consumer is taking benzodiazepines for anxiety or sleep, the addition of ashwagandha may increase the severity of those effects. Careful dose adjustment and monitoring should occur to minimize the risk of excessive sedation [3, 6].

Zolpidem and other hypnotic medications produce sleep by activating GABA receptors. Ashwagandha produces a mild soporific effect. Together they may increase the duration and intensity of sedation. In particular, this combination may exacerbate excessive morning sleepiness/grogginess (“hangover”) and may increase the risk of side effects such as confusion or sleep-related behaviors. Although there are no documented case reports of interactions between ashwagandha and hypnotics, consumers should be cautioned that the use of ashwagandha concurrently with a strong sedative like zolpidem may increase the risk of

unintended sedation. It would be reasonable to avoid concurrent use at bedtime, or to use lower doses of either medication [6, 7].

The primary concern is that ashwagandha will add to the sedative effects of other CNS depressants and/or anxiolytics. The combination of ashwagandha with either alcohol or a prescribed sedative will likely increase drowsiness; the individual's judgment and decision-making abilities will likely be impaired; and there is a risk of respiratory depression when the two are taken together. There are no formal studies to evaluate the ashwagandha–alcohol interaction; however, in line with conventional medical wisdom, individuals who take sedating herbal products should avoid heavy drinking. While individuals taking ashwagandha should exercise caution when consuming alcohol – particularly if they experience unusual sleepiness – the primary concern is to alert patients to the potential for increased drowsiness and slower reaction time when ashwagandha is combined with prescription sedatives [6, 16, 17].

In general, ashwagandha appears to be safe for the majority of healthy adults at typical dosing levels. All clinical trials and safety studies assessing the short- to intermediate-term usage of ashwagandha have reported minimal to no serious adverse events. Side effects that occur as a result of ashwagandha are typically mild and temporary. They include gastrointestinal distress, drowsiness, and dizziness. It is worth noting that, since the primary effect of ashwagandha is to induce sedation, somnolence (drowsiness) is among the most frequently cited side effects. Only a small number of participants in the large trials assessing ashwagandha root extracts experienced any statistically significant laboratory abnormality or long-term issue. Furthermore, no clinically relevant changes were identified in liver enzyme activity, renal function, or blood counts during normal use of ashwagandha, suggesting a high degree of safety [4, 10, 11].

Finally, ashwagandha has a relatively non-toxic pharmacokinetic profile. Studies have shown that ashwagandha does not significantly inhibit any of the major cytochrome P450 enzymes (such as CYP3A4 or CYP2D6) in humans. Therefore, it is unlikely to affect the blood concentrations of most prescription medications through metabolic interference [11,15, 18]. In comparison, Rhodiola rosea contains compounds that cause marked inhibition of CYP2D6, resulting in documented interactions with prescription medications [19, 20]. Consequently, ashwagandha is viewed as a safer option than Rhodiola with regard to the potential for drug-herb metabolism interactions [19, 20]. However, the major caution regarding ashwagandha

remains its sedative/anti-anxiety effects. As mentioned above, ashwagandha does not significantly influence the breakdown rates of most other drugs; rather, it shares some pharmacodynamic targets (GABA signaling) with those drugs. Therefore, whenever ashwagandha is used in conjunction with other CNS depressants (including prescription medications such as benzodiazepines or substances such as alcohol), users need to monitor their overall level of CNS depression and adjust accordingly. Ashwagandha's interaction profile is advantageous from a metabolic standpoint; however, given the sedative effects inherent in ashwagandha, combining it with other sedatives or sleep aids will likely increase the user's risk of becoming overly sleepy and/or losing coordination [3, 6, 17].

4. Rhodiola rosea

Rhodiola rosea, commonly known as golden root, is a renowned herbal adaptogen used to enhance the body's resilience to stress [1, 2]. As an adaptogen, it helps maintain homeostasis during physical or mental stress, improving energy, focus, and reducing fatigue [1]. Rhodiola's anti-stress effects are linked to modulation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to more balanced cortisol levels and a normalized stress response [1, 13]. Clinically, this translates to reduced stress-induced symptoms and improved mental and physical performance under challenging conditions [1, 21]. Rhodiola is well-tolerated and considered non-toxic at recommended doses[1, 22].

Mechanisms of Action on Neurotransmitters

Rhodiola exerts multiple effects on the central nervous system through its active phytochemicals (such as rosavin, salidroside, and rosiridin) [1, 24]. The main mechanism of action is the influence on monoamine neurotransmitters. Rhodiola has been shown to increase levels of serotonin and dopamine in the brain, as well as norepinephrine, which contributes to its antidepressant and stimulant properties [21, 24]. It achieves this partly by inhibiting monoamine oxidases (MAO-A and MAO-B), the enzymes responsible for breaking down these neurotransmitters [24]. By blocking MAO-A, Rhodiola can elevate serotonin and norepinephrine availability, while MAO-B inhibition can increase dopamine levels. Additionally, some studies suggest Rhodiola may enhance the sensitivity of certain receptors or facilitate neurotransmitter release [24]. Through these combined actions, Rhodiola supports mood elevation, cognitive function, and may alleviate mild depressive symptoms [21, 25].

However, these same neurochemical effects underlie important interactions with other drugs that affect monoamine levels.

Interactions with Antidepressants (Serotonin Syndrome Risk)

Because Rhodiola increases serotonin levels and inhibits its breakdown, concurrent use with antidepressants - especially SSRIs or SNRIs that also raise serotonin - can potentiate serotonergic activity [8, 21]. This raises concern for serotonin syndrome, a potentially serious condition caused by excessive serotonin stimulation [8]. Patients taking Rhodiola alongside SSRIs/SNRIs have reported symptoms consistent with serotonin syndrome, such as heightened restlessness, tremors, rapid heart rate, and autonomic instability[8]. For instance, a case report documented a patient on the SSRI paroxetine who developed agitation and tremors after adding Rhodiola, suggesting a serotonergic interaction [8]. Although not every combination will result in toxicity, these findings indicate a real risk. Caution is advised when combining Rhodiola with any antidepressant; healthcare providers often recommend against this combination or require close monitoring [7, 8]. If used together, patients should be educated about early signs of serotonin surplus (e.g. excessive sweating, jitteriness, confusion) and instructed to seek medical attention if such symptoms appear. In summary, Rhodiola's monoamine-enhancing properties, while beneficial for mood, can dangerously amplify antidepressant effects, so combining them should be done only under professional guidance, if at all [7, 8, 21].

Interactions with Stimulants and Sympathomimetics

Rhodiola can increase alertness and reduce fatigue, which is generally mild, but when combined with stimulant substances (such as caffeine, amphetamines like Adderall, or other energizing supplements), there is a risk of additive overstimulation [1, 21, 24]. It increases risk of additive activation of the central nervous system and cardiovascular system, which may manifest as increased heart rate, increased blood pressure, anxiety, or insomnia [7, 17]. Although formal drug interaction studies between rhodiola rosea and prescription stimulants are lacking, general principles of pharmacodynamic interactions and current phytotherapy guidelines support a cautious approach [7, 17]. Therefore, when using rhodiola rosea in individuals already receiving stimulant pharmacotherapy, it is prudent to start treatment with low doses, monitor for signs of overstimulation (e.g., marked nervousness, palpitations, sleep disturbances), and adjust treatment if such symptoms occur. In general, rhodiola rosea is best used as monotherapy for

stress-related fatigue, rather than in combination with other strongly stimulating products [7, 17].

Effects on Cytochrome P450 Enzymes and Pharmacokinetic Interactions

Beyond pharmacodynamic interactions, Rhodiola can affect drug metabolism pathways, leading to pharmacokinetic interactions. Research indicates that Rhodiola rosea extracts and several of its isolated compounds can inhibit cytochrome P450 enzymes, particularly CYP2D6 and CYP3A4, which are among the major enzymes that metabolize many medications [19, 20]. In vitro studies have identified compounds like rhodionin and rhodiosin from Rhodiola as potent inhibitors of CYP2D6, capable of significantly reducing this enzyme's activity [19]. Likewise, Rhodiola preparations (notably certain alcohol tinctures) have demonstrated inhibition of CYP3A4 [20, 23]. What this means clinically is that Rhodiola might slow the clearance of drugs that rely on these enzymes, causing higher blood concentrations and prolonged effects of the co-administered drugs [16]. For example, if taken with a medication primarily metabolized by CYP3A4 (such as certain statins, calcium channel blockers, or immunosuppressants) or by CYP2D6 (such as many antidepressants, antipsychotics, or beta-blockers), Rhodiola could increase that drug's exposure, potentially enhancing both its desired effects and side effects [16, 19, 23]. Conversely, there is a risk that stopping Rhodiola could lower levels of those drugs if the body's enzyme activity rebounds. Although human studies are somewhat limited, one clinical finding showed a commercial Rhodiola product (Arctic Root) significantly inhibited CYP3A4/2D6 activity in healthy volunteers, confirming that in vivo interactions can occur [20, 23]. It is also noted that Rhodiola might influence other metabolic proteins like P-glycoprotein, which could alter drug absorption and distribution [16]. In practice, patients on narrow therapeutic index drugs metabolized by CYP3A4 or 2D6 should use Rhodiola cautiously. Physicians and pharmacists should be informed of Rhodiola use so they can monitor for signs of altered drug levels, such as unexpected sedation, overactivity, or toxicity [5, 16, 23]. Until more data are available, the safest course is to avoid combining Rhodiola with critical medications known to be sensitive to metabolism changes, or if necessary, to adjust doses under medical supervision.

5. Practical recommendations for the use of adaptogens in psychiatric patients

Adaptogens should not be recommended without a prior comprehensive clinical evaluation. A clinician should review the patient's complete prescription history, including all prescribed psychotropics, OTC medications and supplements [5, 6, 17]. Particular attention should be paid to the use of antidepressants (SSRIs, SNRIs, tricyclics), mood stabilizers, benzodiazepines, non-benzodiazepine hypnotics and other CNS-active agents [6, 7, 17]. Chronic conditions that may alter the metabolism, absorption or distribution of supplements (e.g. liver or kidney disease, epilepsy, cardiovascular disease) also need to be considered [16, 18]. In addition, clinicians should identify high-risk groups such as patients with polypharmacy, older adults with age-related changes in pharmacokinetics and pharmacodynamics, and those treated with drugs that have a narrow therapeutic index (e.g. lithium, selected antiepileptics, certain antiarrhythmics). In these populations, even mild herb-induced changes in medication absorption, distribution, metabolism or effect may result in severe adverse reactions [5, 6, 16].

Based on the existing literature about *Withania somnifera* (ashwagandha) and *Rhodiola rosea*, we propose a practical decision-making process. Ashwagandha appears less likely than Rhodiola to cause clinically significant cytochrome P450-mediated herb-drug interactions [3,14,15], but it has GABA agonist properties and produces sedative and anxiolytic effects [3, 9, 14, 15]. Consequently, when prescribing ashwagandha to patients already treated with benzodiazepines, Z-drugs or other CNS depressants, clinicians should use a cautious dosing strategy and closely monitor daytime alertness and functioning [3, 6, 7, 16]. In contrast, *Rhodiola rosea* exerts stimulating, monoaminergic effects and inhibits CYP2D6 and CYP3A4, two key cytochrome P450 enzymes involved in the metabolism of many psychotropics, including antidepressants, antipsychotics and beta-blockers [1, 19, 21]. Rhodiola may therefore both increase the risk of excessive serotonergic activity when combined with SSRIs or SNRIs, contributing to serotonin toxicity, and raise plasma levels of these drugs by inhibiting their metabolism [6, 8, 17, 21, 26]. Clinicians can conceptualize the relationship between psychotropic classes, specific adaptogens and interaction risks using a simple matrix that links each drug class to each adaptogen and the predominant interaction pattern: for example, SSRI + Rhodiola = high risk of serotonergic excess and metabolic inhibition; SSRI + ashwagandha = moderate to high risk of additive sedation and cognitive blunting; benzodiazepine or sedative-hypnotic + ashwagandha = moderate to high risk of respiratory and CNS depression; Rhodiola

+ CYP2D6- or CYP3A4-dependent agents = moderate to high risk of accumulation and dose-related adverse effects [6, 7, 17].

The use of adaptogens requires careful monitoring and patient education. Ongoing clinical assessment becomes essential once an adaptogen has been initiated. The clinician should be aware of the early warning signs and symptoms of Serotonin Syndrome when an herb (such as Rhodiola) modulates monoamines and the patient is taking an antidepressant [6, 8, 25, 26]. New-onset agitation, tremors, tachycardia, increased sweating, hyperreflexia or altered mental status in a patient who is being treated with an antidepressant should lead to reassessment of the treatment regimen and, if indicated, urgent evaluation. Similarly, because of the sedating properties of ashwagandha or other botanicals, caution is warranted when these are used in combination with hypnotic or anxiolytic medications [7, 14, 15, 17]. Vigilance is required for excessive somnolence, impaired concentration, decreased reaction time or loss of coordination; all of these effects can result in falls, impaired driving ability or reduced work performance. If Rhodiola is used in combination with medications primarily metabolized through CYP2D6 or CYP3A4, a marked increase in the effect of the medication or the development of dose-related side effects may indicate reduced metabolism of the drug [5, 16, 20].

Education of patients about their herbal supplements should be an integral part of the treatment plan [6, 27]. Many psychiatric patients view herbal supplements as “benign natural” products and may initiate additional products for stress, sleep or mood without disclosing this to their psychiatrist [7]. Therefore, the potential for interactions between herbal supplements and psychotropic medications should be clearly explained, and patients should be advised to report any new or unusual symptoms after starting an herbal product [5, 6, 7]. They should also be discouraged from adding further sedative or adaptogenic supplements to an existing regimen and encouraged to inform their psychiatrist, primary care physician and pharmacist about all herbal and dietary supplements to allow prospective identification of possible interactions [5, 7, 27]. Several common clinical scenarios illustrate how these principles may be applied in practice. In a patient with major depressive disorder stabilized on an SSRI, prescribing Rhodiola represents a high-risk choice because of its monoaminergic profile and inhibition of CYP2D6 and CYP3A4, whereas ashwagandha is metabolically safer but its sedative properties limit its use as a pharmacologically “neutral” agent, particularly in the presence of fatigue, cognitive

slowing or concomitant CNS depressants [1, 20, 21, 26]. In a patient with primary insomnia treated with zolpidem or a benzodiazepine, adding ashwagandha may improve sleep onset and duration at the cost of increased residual daytime sedation and functional impairment, requiring a careful balance of benefit versus risk and potential adjustment of drug or adaptogen doses [3, 6, 7, 16, 17]. In bipolar disorder or in individuals with a history of hypomania, the activating effects of Rhodiola warrant a cautious or avoidant approach, whereas ashwagandha, although behaviourally less activating, should still be monitored for mood destabilization [6, 7, 17, 21].

Although the literature on the neuropsychotropic effects of adaptogenic substances is expanding, significant knowledge gaps remain. Most available data come from studies in healthy volunteers or individuals with mild to moderate stress-related symptoms rather than patients with severe, comorbid psychiatric disorders and complex pharmacotherapy [2, 14]. Controlled trials evaluating the safety and efficacy of ashwagandha, Rhodiola and other adaptogens as adjuncts to psychotropic medications are limited, dosing guidelines specific to psychiatric populations are lacking, and there is substantial variability between preparations in terms of standardization, bioactive content and quality control [2, 15, 25]. Future research should prioritise high-risk drug-herb combinations such as Rhodiola with SSRIs/SNRIs, ashwagandha with long-term benzodiazepines or Z-drugs, and adaptogens with mood stabilizers or antipsychotics, as well as long-term observational studies and comparative work on different extract types and standardization methods to better define interaction risk.

6. Conclusions

Botanical adaptogens (e.g., Withania somnifera; Rhodiola rosea) are positioned in a "grey zone" for individuals who may choose to take them as complementary care to manage stress, mood or sleep issues versus formally prescribed treatments by mental health professionals. As suggested by the data gathered in this literature review, there is substantial evidence that adaptogens influence both stress response mechanisms and mood/sleep quality in certain populations. However, the pharmacological activity of adaptogens allows them to interact with psychotropic medications, which may significantly impact efficacy, tolerability, and potential toxicity in certain patients. In psychiatric populations, ashwagandha appears to be associated

with lower metabolic risks compared to rhodiola, however, the GABA-nergic and sedative properties of ashwagandha warrant caution in all patients currently treated with CNS depressants.Rhodiola rosea, in addition to inhibiting CYP450 isoenzymes, provides monoaminergic stimulation but is associated with an increased risk of serotonergic and pharmacokinetic interactions. Taken together, these findings suggest that adaptogen use should not be viewed as a neutral "add-on" to conventional treatments but should be integrated into standard clinical practice through routine herbal research, individual risk assessment, and regular monitoringTherefore, further research using controlled clinical trials in patients undergoing psychopharmacological treatment, along with additional studies focusing on standardized preparations and specific herbal combinations, will be necessary to establish more comprehensive guidelines for the safe and evidence-based use of adaptogens in contemporary psychiatric practice.

Disclosure

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References

1. Anghelescu IG, Edwards D, Seifritz E, Kasper S. Stress management and the role of Rhodiola rosea: a review. Int J Psychiatry Clin Pract. 2018;22(4):242-252.

2. Todorova V, Ivanov K, Delattre C, Nalbantova V, Karcheva-Bahchevanska D, Ivanova S. Plant adaptogens – history and future perspectives. Nutrients. 2021;13(8):2861.

3. Speers AB, Cabey KA, Soumyanath A, Wright KM. Effects of Withania somnifera (ashwagandha) on stress and the stress-related neuropsychiatric disorders anxiety, depression, and insomnia. Curr Neuropharmacol. 2021;19(9):1468-1495.

4. Verma N, Gupta SK, Tiwari S, Mishra AK. Safety of ashwagandha root extract: a randomized, placebo-controlled study in healthy volunteers. Complement Ther Med. 2021;57:102642.

5. Zhang Y, Man Ip C, Lai YS, Zuo Z. Overview of current herb-drug interaction databases. Drug Metab Dispos. 2022;50(1):86-94.

6. Czigle S, Nagy M, Mladěnka P, Tóth J. Pharmacokinetic and pharmacodynamic herb-drug interactions: Part I. Herbal medicines of the central nervous system. PeerJ. 2023;11:e16149.

7. Lacerda GFM, Oliviera PC, Vital MABF, Slomp H Jr, Galduróz JCF, Andreatini R. Phytotherapy in psychiatry: why psychiatrists should know about it. Acta Neuropsychiatr. 2024;36(4):189-194.

8. Maniscalco I. The interaction of Rhodiola rosea and antidepressants: a case report. Neuropsychiatrie. 2015;29(1):36-38. doi:10.1007/s40211-014-0124-8.

9. Pandit S, Srivastav AK, Sur TK, Chaudhuri S, Wang Y, Biswas TK. Effects of Withania somnifera extract in chronically stressed adults: a randomized controlled trial. Nutrients. 2024;16(9):1293.

10. Majeed M, Nagabhushanam K, Mundkur L. A standardized ashwagandha root extract alleviates stress, anxiety, and improves quality of life in healthy adults by modulating stress hormones: results from a randomized, double-blind, placebo-controlled study. Medicine

(Baltimore). 2023;102(41):e35521.

11. Wróbel-Biedrawa D, Podolak I. Anti-neuroinflammatory effects of adaptogens: a mini-review. Molecules. 2024;29(4):866.

12. Arumugam V, Vijayakumar V, Balakrishnan A, Bhandari RB, Boopalan D, Ponnurangam R, et al. Effects of ashwagandha (Withania somnifera) on stress and anxiety: a systematic review and meta-analysis. Explore (NY). 2024;20(6):103062. doi:10.1016/j.explore.2024.103062.

13. Tóth-Mészáros A, Garmaa G, Hegyi P, Bánvölgyi A, Fenyves B, Fehérvári P, et al. The effect of adaptogenic plants on stress: a systematic review and meta-analysis. J Funct Foods. 2023;108:105695.

14. Tandon N, Yadav SS. Safety and clinical effectiveness of Withania somnifera (Linn.) Dunal root in human ailments. J Ethnopharmacol. 2020;255:112768.

15. Mandlik Ingawale DS, Namdeo AG. Pharmacological evaluation of ashwagandha highlighting its healthcare claims, safety, and toxicity aspects. J Diet Suppl. 2021;18(2):183-226.

16. Cheng W, Xia K, Wu S, Li Y. Herb-drug interactions and their impact on pharmacokinetics: an update. Curr Drug Metab. 2023;24(1):28-69.

17. Sarris J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. Phytother Res. 2018;32(7):1147-1162.

18. Daniel WA, Bromek E, Danek PJ, Haduch A. The mechanisms of interactions of psychotropic drugs with liver and brain cytochrome P450 and their significance for drug effect and drug-drug interactions. Biochem Pharmacol. 2022;199:115006.

19. Xu W, Zhang T, Wang Z, Liu T, Liu Y, Cao Z, Sui Z. Two potent cytochrome P450 2D6 inhibitors found in Rhodiola rosea. Pharmazie. 2013;68(12):974-976.

20. Thu OK, Nilsen OG, Hellum B. In vitro inhibition of cytochrome P450 activities and quantification of constituents in a selection of commercial Rhodiola rosea products. Pharm Biol. 2016;54(12):3249-3256.

21. Amsterdam JD, Panossian AG. Rhodiola rosea L. as a putative botanical antidepressant. Phytomedicine. 2016;23(7):770-783.

22. Pu WL, Zhang MY, Bai RY, Sun LK, Li WH, Yu YL, et al. Anti-inflammatory effects of Rhodiola rosea L.: a review. Biomed Pharmacother. 2020;121:109552.

23. Firenzuoli F, Villa G, Firenzuoli F. Rhodiola rosea L.: potential herbal-drug interactions in perioperative medicine. J Clin Anesth. 2024;97:111544.

24. Juřica J, Koupá T. [Rhodiola rosea and its neuropsychotropic effects]. Ceska Slov Farm. 2016;65(3):87-93.

25. Concerto C, Infortuna C, Muscatello MRA, Bruno A, Zoccali R, Chusid E, et al. Exploring the effect of adaptogenic Rhodiola rosea extract on neuroplasticity in humans. Complement Ther Med. 2018;41:141-146.

26. Gao L, Wu C, Liao Y, Wang J. Antidepressant effects of Rhodiola capsule combined with sertraline for major depressive disorder: a randomized double-blind placebo-controlled clinical trial. J Affect Disord. 2020;265:99-103.

27. Future trends in integrated mental healthcare [Internet]. Elsevier; 2024. Available from: https://www.sciencedirect.com/science/chapter/monograph/abs/pii/B9780443439087000045. Accessed November 10, 2025.