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SYSTEMATIC REVIEW ARTICLE

Herb-drug Interactions in Neuropsychiatric Pharmacotherapy – A Review of Clinically Relevant Findings

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Abstract: The management of neuropsychiatric disorders relies heavily on pharmacotherapy. The use of herbal products as complimentary medicine, often concomitantly, is common among patients taking prescription neuropsychiatric drugs. Herb-drug interaction, a clinical consequence of this practice, may jeopardize the success of pharmacotherapy in neuropsychiatry. Besides the well-known ability of phytochemicals to inhibit and/or induce drug-metabolizing enzymes and transport proteins, several phytoconstituents are capable of exerting pharmacological effects on the central nervous system. This study reviewed the relevant literature and identified 13 commonly used herbal products - celery, echinacea, ginkgo, ginseng, hydroxycut, kava, kratom, moringa, piperine, rhodiola, St. John's wort, terminalia/commiphora ayurvedic mixture and valerian - which have shown clinically relevant interactions with prescription drugs used in the management of neuropsychiatric disorders. The consequent pharmacokinetic and pharmacodynamic interactions with orthodox medications often result in deleterious clinical consequences. This underscores the importance of caution in herb-drug co-medication.

Keywords: Complimentary medicine, herb-drug interaction, neuropsychiatry, pharmacotherapy, St. John's wort, antipsychotic drug.

1. INTRODUCTION

Herbal products are globally popular as complementary and/or alternative medicine [1]. The 2019 Herb Market Report estimates that $9.6 billion was spent on herbal supplements in the United States alone, showing an increase of 8.6% in sales over the previous year [2]. Furthermore, the global financial investment in herbal medicine is expected to reach $129 billion by the year 2023 [3]. Among several reasons, including culture and accessibility, the general perception of safety and absence of adverse effects with the use of herbal medicines is considered the overbearing factor responsible for the popularity of herbal medicine [4, 5]. However, like conventional drugs, the phytochemical constituents of herbs are capable of exerting pharmacological changes in the human body. Thus, a toxic response to herbal ingestion is not uncommon.

Data on the prevalence of herb-drug combination use may vary based on such factors as age, disease, health education, culture and geography. The data from the 2015 National Consumer Survey on the Medication Experience and Pharmacists' Roles, as analyzed by Rashrash *et al.* showed that the practice of herbal co-medication with prescription drugs cut across various patient demographics, with 38% of respondents reporting concomitant herbal use [6]. A study reported 36.4% prevalence of concomitant Chinese medicine/antipsychotic drug use [7], while a similar survey found a 33.6% prevalence among British community-dwelling older adults [8]. Depending on other factors, these figures have been reported to be as high as 80% [9, 10]. Thus, it can be conservatively estimated that one in three patients taking prescription medicine also consumes herbal supplements concurrently.

While herbal medicine is generally not replacing prescription medicine, the practice of concurrent use of herbal and prescription medicines raises concerns of herb-drug interactions (HDIs). Like drug-drug interactions, HDIs occur when the expected systemic disposition and/or effect of an administered drug is altered by, or due to, the presence/action of a concomitantly administered herbal product.

Since the accidental discovery of the ability of grapefruit juice to alter the pharmacokinetic profiles of felodipine through the inhibition of cytochrome P450 (CYP) and P-glycoprotein (P-gp), more studies have elucidated various mechanisms of HDI [11]. Besides the inhibitory and inductive effects of phytochemicals on drug-metabolizing enzymes (DMEs) and transport proteins, the intrinsic ability of phytoconstituents to interact with physiologic receptors can

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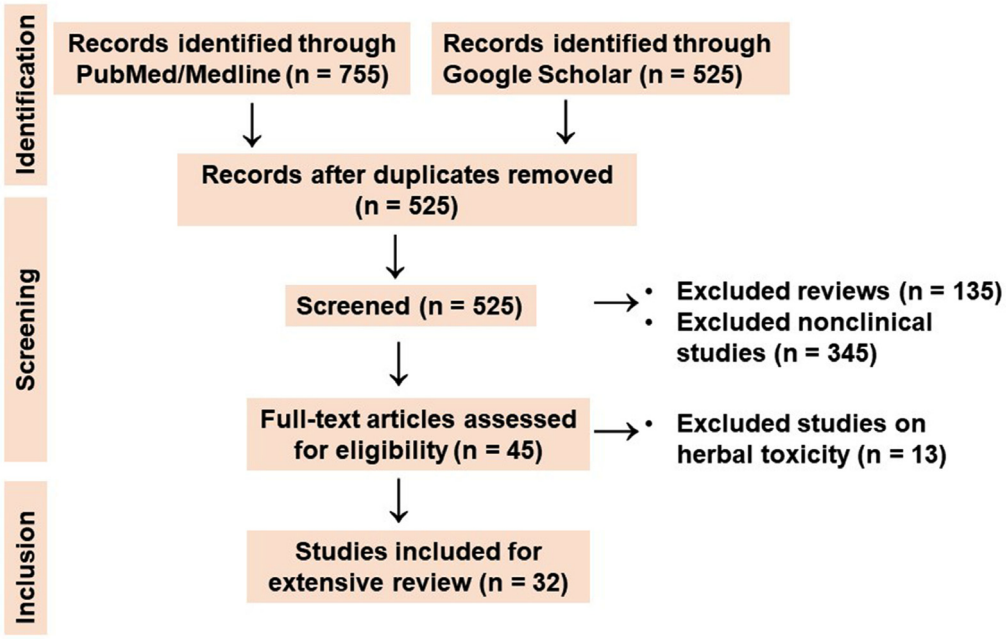

Fig. (1). Search strategy and search results for herbal interactions in neuropsychiatry.

precipitate antagonistic, additive, or synergistic pharmacodynamic responses in the presence of prescription drugs. While most HDIs might be clinically inconsequential, many others are deleterious and lead to therapy failure and/or toxic manifestations [12, 13].

For several reasons, patients with chronic diseases, including neurological and psychiatric disorders, continue to seek help from herbal medicine, some in addition to their prescription drugs [14, 15]. Achieving stable control of symptoms with pharmacotherapy in neuropsychiatry takes time and requires professional skills in dose titration and maximization while avoiding toxicity. The potential of herbal products to disrupt this careful balance could be dangerous to patients and complicate management strategies. Several drugs used in neuropsychiatry are substrates of CYPs, making them potential victims of HDIs. Herbal products with claimed beneficial effects in mental health may elicit pharmacodynamic changes via similar mechanisms to prescription medicines. The potential for synergy or antagonism is, therefore, a cause for clinical concern in herb-drug combination therapies.

The purpose of this paper is to provide a review of the current evidence for HDIs in the pharmacotherapy of neuropsychiatric disorders. It is aimed that the review, with a focus on clinically relevant interactions, will be of interest to the health-consuming public, researchers, and healthcare professionals, particularly those who manage neuropsychiatric disorders.

2. METHODS

A systematic review of the literature was conducted to identify and provide an overview of individual herbal products that have shown clinically relevant HDIs. Searches were conducted using the PubMed, Medline, and Google Scholar databases for original clinical studies, including case reports and case series, where the focus is on HDIs. The following search terms and the combinations thereof were used: herbal medicine, herbal products, herbal interactions, psychiatry, neuropsychiatry, pharmacotherapy. Further searches were conducted with combinations of identified individual herbal products commonly used in neuropsychiatry and individual neuropsychiatric drugs. Retrieved studies were screened for inclusion which was based on the availability of the publications in the English language and the performance of the studies in human subjects. Studies included for extensive reviews were not limited by the time or place of study/publication.

3. RESULTS

A total of 525 publications were retrieved from the searches, with only 32 found to meet inclusion criteria for extensive review (Fig. **1**). Overall, 13 herbal products were identified to have shown clinically relevant HDIs in neuropsychiatry. These are celery, echinacea, ginkgo, ginseng, hydroxycut, kava, kratom, moringa, piperine, rhodiola, St. John's wort, terminalia/commiphora ayurvedic mixture and valerian. A summary of the reviewed studies is presented in Table **1**.

3.1. Celery

Celery *(Apium graveolens*) is an aromatic plant whose fresh herbs are commonly used in salad preparations and extracted into juices. Celery root and leaf extracts are consumed as medicinal supplements in capsule, tablet, and liquid formulations. The plant is a member of the umbelliferous family of herbs which contains phytoestrogens, the natural estrogen-like phytochemicals capable of directly binding and activating estrogen receptors. Thus, celery supplements are popular for the management of low estrogen states, such as menopause. Phytoestrogens and other bioactive components of celery can interact with the DMEs, including those in the CYP450 family. Potent inhibition of the several isoforms of CYP by celery extracts, including active

Table 1. Clinically relevant herbal interactions with neuropsychiatric drugs.

Herb Product	Neuropsychiatric Drug	Study Type and Description	Findings	Putative Mechanism	References
Celery extracts	Venlafaxine	Case report	Patient stably managed for depression with venlafaxine and SJW for depression developed acute episodes of mania 48 h after initiating oral celery root capsules for menopause. Higher plasma level of venlafaxine was observed.	Celery root inhibits CYP2D6, leading to increased levels of CYP2D6 substrates, such as venlafaxine.	[16]
Echinacea	Midazolam	Open-label, crossover	Echinacea increased the systemic clearance of midazolam by 34%, decreasing the AUC by 23%.	Echinacea induces CYP3A4 and P-gp.	[17]
Ginkgo biloba	Bupropion	Two-period, open-labeled, fixed-sequence design	The use of GBE for 14 days did not significantly change the overall AUC of bupropion but significantly reduced the $t_{1/2}$ and increased the C_{max} of its metabolite.	GBE induces various hepatic CYP isoforms, including CYP2B, which is responsible for bupropion metabolism.	[18]
Ginkgo Biloba	Risperidone	Case report	Patient with schizophrenia on risperidone for three years experienced priapism after taking GBE.	GBE is an inhibitor of CYP450 2D6 and 3A4, both of which metabolize risperidone. This resulted in increased serum concentrations of risperidone, resulting in priapism, a known dose-dependent adverse effect of risperidone.	[19]
Ginkgo Biloba	Trazodone	Case report	Patient with Alzheimer's refractory to multiple drugs eventually had GBE/trazodone combination. Patient fell into coma on Day-3. The administration of flumazenil awoke the patient.	Flavonoids GBE possesses GABAergic activity as partial agonists. They also can induce CYP3A4 enzymes, leading to enhanced production of active GABAnergic metabolites from trazodone.	[20]
Ginkgo	Valproate	Case report	Patient with a history of epilepsy and stabilized on sodium valproate and phenytoin experienced a fatal breakthrough seizure, with autopsy revealing subtherapeutic serum levels for both drugs. Patient recently initiated ginkgo supplementation.	Ginkgo induced the metabolism of the anticonvulsant drugs leading to subtherapeutic plasma levels. Additionally, an epileptogenic neurotoxin has been identified in ginkgo nuts.	[21]
Ginkgo	Valproate	Case series	Two patients with recurrent seizures otherwise had well-controlled epilepsy until the start of ginkgo supplements. Seizures ceased upon ginkgo discontinuation.	Ginkgo induced the metabolism of valproate. Some phytochemicals in ginkgo may be epileptogenic.	[22]
Ginkgo	Donepezil	Open-label, crossover	The steady-state pharmacokinetics of donepezil in 14 in-patients with Alzheimer's disease was analyzed before and after 30-day ginkgo supplementation. No significant difference was observed.	The known effect of GBE on CYPs did not translate to any significant HDI with donepezil.	[23]
Ginkgo	Midazolam	Open-label, crossover	GBE caused 25 % increase in the AUC, and 26% decrease in the oral clearance of midazolam.	GBE inhibited the CYP3A4-mediated metabolism of midazolam.	[24]
Ginkgo	Midazolam	Open-label, crossover	Concomitant use of GBE was associated with 34% and 31% decrease in the AUC and C_{max} of midazolam respectively.	CYP3A4-mediated metabolism of midazolam was inhibited by GBE.	[25]
Ginkgo	Diazepam	Open-label, crossover	GBE did not significantly alter the PK parameters of diazepam in healthy subjects.	GBE modulate CYPs *in vitro*. Short-term use did not affect the clinical PK of diazepam.	[26]
Ginseng	Midazolam	Open-label, crossover	*P. ginseng* significantly reduced the AUC, half-life, and Cmax of midazolam in healthy individuals.	*P. ginseng* induces CYP3A4/5; therefore, will increase elimination of CYP3A4/5 substrates, such as midazolam.	[27]

(Table 1) contd….

Herb Product	Neuropsychiatric Drug	Study Type and Description	Findings	Putative Mechanism	References
Ginseng	Phenelzine	Case report	Patient with a history of depression was started on phenelzine while taking ginseng. Patient became active and extremely optimistic while experiencing insomnia, tension headaches, and visual hallucinations. Once the patient discontinued phenelzine, depression returned with no other signs and symptoms.	A pharmacodynamic interaction occasioned by additive stimulant activities of phenelzine and ginseng. Extracts of *P. ginseng* inhibits cyclic AMP phosphodiesterase, thus enhancing the psychoactive effect in combination with monoamine oxidase inhibitors such as phenelzine.	[28]
Hydroxycut	Citalopram	Case report	A patient being treated for depression with citalopram developed reversible cerebral vasoconstriction syndrome (RCVS) during concurrent supplementation with Hydroxycut for weight loss.	Additive or synergistic CNS effects of citalopram and Hydroxycut.	[29]
Kava	Alprazolam	Case report	Concomitant consumption led to coma.	Kavalactones, the primary active phytochemicals in kava, are potent inhibitors of CYP enzymes.	[30]
Kava	Levodopa	Case report	After 10 days of initiating Kava, patient experienced increased frequency and duration of "off" episodes, indicating a reduced effectiveness of levodopa.	Central dopaminergic antagonism.	[31]
Kratom	Quetiapine	Case report	Patient was found deceased with a toxic blood concentration of quetiapine in conjunction with the qualitative presence of mitragynine.	Mitragynine is a competitive inhibitor of CYP3A4, and when used together, can lead to the accumulation of CYP3A4 substrates like quetiapine.	[32]
Morinda citrifolia (noni juice)	Phenytoin	Case report	Patient with epilepsy, who had been treated with phenytoin for over 10 years, developed poor seizure control after consumption of noni juice.	Phytoconstituents of M. citrifolia induces CYP2C9, leading to increased phenytoin clearance.	[33]
Piperine	Midazolma	Placebo-controlled	Pretreatment with piperine significantly increased the half-life, and decreased the clearance of midazolam, compared to placebo.	Piperine inhibits the CYP-dependent metabolism of midazolam.	[34]
Piperine	Phenytoin	Open-label exploratory	Single dose piperine in patients at steady state with phenytoin significantly increased the mean plasma AUC and Cmax of phenytoin.	Piperine inhibits the CYP2C9-dependent metabolism of phenytoin.	[35]
Piperine	Carbamazepine	Open-label exploratory	Single dose piperine increased the AUC and the Css of carbamazepine while decreasing the elimination rate.	Piperine inhibited CYP enzymes.	[36]
Rhodiola rosea	Paroxetine	Case report	Patient with recurrent depression being treated with paroxetine developed serotonergic syndrome after self-medicating with rhodiola rosea.	Rhodiola rosea has serotonergic activity and, when combined with selective serotonin reuptake inhibitors, can lead to the development of serotonin syndrome.	[37]
SJW	Alprazolam	Open-label crossover, fixed treatment	A 14-day pretreatment with SJW caused a statistically significant increase in the clearance, decrease in the AUC, and decrease in the $t_{1/2}$ of alprazolam	SJW induces CYP3A4, the enzyme that predominantly metabolizes alprazolam.	[38]
SJW	Amitriptyline	Open-label crossover	The steady state pharmacokinetics of amitriptyline was compared pre- and post-SJW treatment. SJW significantly reduced the AUC of amitriptyline.	SJW induces P-gp and CYP3A4 leading to reduced absorption and increased clearance of amitriptyline.	[39]
SJW	Bupropion	Case report	Patient on SJW for years experienced oro-facial dystonia over 5 months after taking bupropion.	Combination of SJW and bupropion exert additive inhibition of serotonin reuptake, with additional enhanced dopaminergic effects such as dystonia.	[40]

(Table 1) contd….

Herb Product	Neuropsychiatric Drug	Study Type and Description	Findings	Putative Mechanism	References
SJW	Clozapine	Case report	Patient with schizophrenia on clozapine for 6 months showed decreased plasma clozapine concentration and deterioration of psychiatric condition after taking SJW.	SJW induces CYP3A4-dependent metabolism and P-gp-mediated efflux of clozapine, leading to subtherapeutic clozapine levels.	[41]
SJW	Midazolam	Open-label crossover	SJW was associated with a 2.7-fold increase in the oral clearance, and a 50% reduction in Cmax, and a 44% reduction in t1/2 of midazolam	SJW induces CYP3A4 and P-gp leading to reduced absorption and increased metabolism of midazolam.	[42]
SJW	Paroxetine	Case report	Patient with chronic depression combined paroxetine and SJW resulting in incoherency, nausea, weakness, fatigue, and limp muscle tone, which are consistent with serotonin syndrome.	Additive inhibition of serotonin reuptake by SJW and paroxetine, led to serotonin syndrome.	[43]
SJW	Sertraline and nefazodone	Case series	Series of 5 reports of patients with depression/anxiety being treated with sertraline or nefazodone; and who started taking SJW. Each of the patients experienced signs and symptoms of serotonin syndrome within 2-4 days of beginning SJW. Discontinuation of the combination resolved the symptoms.	SJW, when taken in combination with a serotonin and norepinephrine reuptake inhibitor like nefazodone, can induce serotonin syndrome.	[44]
Terminalia and Commiphora	Sertraline	Case report	Patient well controlled on sertraline experienced two episodes of moderate –severe depression after initiating ayurvedic mixtures, including *Terminalia chebula* and *Commiphora wrightii*. Patient's depression resolved after herbal remedies were discontinued.	Particular contents of the ayurvedic mixture (especially *T. chebula* and *C. wightii)* are thought to induce CYP enzymes leading to increased clearance of sertraline.	[45]
Valerian	Alprazolam	Open-label crossover, fixed treatment	Alprazolam and dextromethorphan (probe substrates of CYP3A4 and CYP2D6, respectively) were administered to volunteers before and after a 14-day pretreatment with valerian. Only the Cmax of alprazolam was significantly increased. No other pharmacokinetic parameters were altered.	Valerian has demonstrated *in vitro* inhibitory activity against CYP enzymes. At doses used in the study, no significant interaction was reported.	[46]
Valerian/ passiflora	Lorazepam	Case report	Patient who has been taking lorazepam for generalized anxiety disorder developed movement disorders after 4 days of concomitant use of valerian/passiflora herbal preparations.	Additive or synergistic CNS effect of lorazepam and valerian/passiflora.	[47]

Abbreviations: GBE – Ginkgo biloba extract; SJW – St. John's wort.

components like methoxsalen, has been reported [48-50]. In animal studies, celery extracts inhibit the metabolism and prolong the effects of CYP substrates [51, 52]. There are currently no randomized controlled clinical trials to highlight the celery-mediated HDIs in humans. However, a published case report highlights a pharmacokinetic interaction between celery and venlafaxine. A 52-year-old patient with a medical history of major depressive disorder, stabilized with venlafaxine and SJW, developed mania and hallucinations within 48 hours after initiating celery supplementation for menopausal issues. The presentations were associated with a higher-than-expected plasma level of venlafaxine. The discontinuation of celery resolved the patient's symptoms. Anecdotal pieces of evidence like this not only highlight the reality and severity of the consequences of HDIs, they underscore the importance of further studies to guide clinical decisions.

3.2. Echinacea

Echinacea is a commonly used herbal preparation as complementary treatment for respiratory infections and common cold. Although there are nine common species of *Echinacea,* most commercial preparations of echinacea in the United States are made from *Echinacea purpurea*. Preclinical studies have suggested echinacea as a modulator of CYP enzymes and P-gp [53, 54]. In an open-label, crossover study, extracts of echinacea increased the systemic clearance of midazolam by 34%, while decreasing the AUC by 23% [17]. The study analyzed the PK of midazolam, a probe substrate of CYP3A4, before and after an 8-day course of echinacea treatment in 12 healthy volunteers. The result suggests that the *in vitro* inhibition of CYP3A4 by echinacea

is potent enough to translate to HDI with drugs that are primarily eliminated by CYP3A4-dependent metabolism.

3.3. Ginkgo

Historically associated with traditional Chinese medicines, ginkgo (*Ginkgo biloba*) is now globally popular and has been a top-seller in the US as a dietary supplement for several health conditions, including anxiety, Alzheimer's dementia, peripheral artery disease, and tinnitus [55, 56]. The commercial ginkgo products currently on the market are prepared mainly by leaf extraction, standardized to contain specified levels of flavones, glycosides, and terpenoids [57]. The flavonoids have been shown to have antioxidant activity, while the ginkgolides have demonstrated an inhibitory effect on the platelet-activating factor with potential cardiovascular benefits [58]. Several controlled clinical studies, as shown by review and meta-analysis of published data, suggest that the use of ginkgo is associated with clinically significant improvement in symptoms of cognition decline and memory loss, anxiety and mood disorders, fatigue and general well-being, as well as cardiovascular disorders [59-61].

The popularity of ginkgo supplements raises concern for concurrent use with prescription medications and the risk for HDIs. Preclinical studies have shown that the phytochemical constituents of ginkgo significantly inhibit/induce DMEs enzymes and transport proteins, including CYPs, UGTs, P-gp, and OATPs [62-69].

Nine clinically relevant HDI reports (5 clinical study, 3 case reports, and 1 case series) were identified with regard to ginkgo biloba extracts (GBE) and neuropsychiatric drugs. Two open-label-crossover studies evaluated the clinical significance of reported *in vitro* CYP3A4 inhibitory activity of GBE using midazolam as probe substrate. In both studies, the concomitant use of GBE was associated with the significant reduction (up to 34%) in the AUC of midazolam in the healthy volunteers [24, 25]. Three other studies evaluated GBE interaction with specific neuropsychiatric drugs. Lei *et al.*, whose study analyzed bupropion in 14 healthy volunteers before and after a 14-day pretreatment with GBE, did not find clinically significant HDIs between GBE and bupropion [18]. Although no significant change was observed in the total bupropion exposure (AUC) in the absence/presence of GBE, the combination was associated with significantly reduced $t_{1/2}$ and increased C_{max} of the major metabolite hydroxybupropion. This result is supported by the inductive effect of GBE on hepatic CYP enzymes, including CYP2B, the isoform responsible for bupropion metabolism.

In the study by Yasui-Furukori *et al.*, the steady-state pharmacokinetics of donepezil in 14 in-patients with Alzheimer's disease was analyzed before and after 30-day ginkgo supplementation with no significant difference observed [23]. In a similar crossover study, GBE did not significantly alter the PK parameters of diazepam in healthy subjects [27]. These mixed results suggest that the modulatory effect of GBE on CYPs may not affect all CYP-substrates equally. The duration of supplementation may also be an important factor for consideration.

A case report of ginkgo-induced HDI involved a patient with a history of schizophrenia who was stable with risperidone treatment for over three years. The patient developed priapism within 2 weeks of initiating GBE for occasional tinnitus. The concurrent use of GBE and risperidone was believed to have increased the serum risperidone concentrations due to CYP inhibition, leading to priapism, a known dose-dependent adverse effect of risperidone. This interaction was further supported by the absence of reoccurrence when the patient discontinued GBE upon treatment and discharge [19].

Another case report involved GBE and trazodone in a patient who had a history of cognitive impairment that was refractory to donepezil and vitamin E therapy. The patient fell into coma (reversible with flumazenil) within three days of initiating concomitant therapy with trazodone and GBE. Multiple plausible explanations for this obvious HDI include GBE-mediated CYP3A4 inhibition with consequent accumulation of trazodone, induction of CYP3A4 enzymes and enhanced production of active GABAnergic metabolites from trazodone, and/or additive GABAnergic effects of GBE [20].

The third case involved a report of fatal seizures due to probable HDIs involving ginkgo [21]. The 55-year-old patient with a history of epilepsy had been managed and stabilized with sodium valproate and phenytoin. He was reported to have experienced a seizure before his death, and the toxicological autopsy results revealed subtherapeutic serum levels for both drugs. The patient had recently initiated ginkgo supplementation, and the apparent HDI was believed to be due to CYP induction by ginkgo resulting in enhanced systemic clearance of the anticonvulsant drugs. Additionally, an epileptogenic neurotoxin has been identified in ginkgo nuts, which may play pharmacodynamic and antagonistic roles in the interactions. Similarly, two patients who were stably managed with valproate and who had been seizure-free for years prior to starting ginkgo supplementation experienced recurrent seizures which ceased upon the discontinuation of ginkgo [22].

Despite the limited reports of clinical HDIs with GBE and neuropsychiatric drugs, it is essential to note that the well-reported CNS effects of GBE make it a potential agent to mediate both pharmacokinetic and pharmacodynamic HDIs with CNS drugs. Caution is generally advised with GBE in patients who are taking prescription medications, especially for CNS disorders.

3.4. Ginseng

Now popular in Western countries, the use of ginseng for medicinal purposes dates back over 5,000 years in traditional Chinese medicine. Used as a complimentary medicine to enhance cognitive function, concentration, and physical endurance, ginseng has also been used as a supplement in the management of depression, fatigue, diabetes, and cancer [70]. Limited clinical studies have shown the potential benefits of these uses [71-78]. While several ginseng species have been identified, the most commonly marketed formulations of ginseng in the US are made from the root extracts of *Panax ginseng* (Korean ginseng) and *Panax quinquefolius* (American ginseng). Ginsenosides, the main active components of ginseng, have demonstrated anti-inflammatory, antioxidant, and cytotoxic effects in laboratory studies [79]. Extracts of ginseng have also been

shown to interact with multiple DMEs and transport proteins via conflicting mechanisms [80-85].

Published studies have reported clinically significant interactions between ginseng and warfarin [86], and imatinib [87]. Minimal interactions between ginseng and neuropsychiatric drugs have been reported in the literature. A common finding is an interaction between ginseng and midazolam, although midazolam is used in these studies as a probe substrate for CYP3A4. The inhibitory and inductive effect of the different phytochemicals in ginseng on CYP3A4 is demonstrated through the observed changes in the AUC and other pharmacokinetic parameters of midazolam in these human studies [27, 88].

A case report documents a patient with chronic depression who was started on phenelzine while taking ginseng. The patient became active and extremely optimistic while experiencing insomnia, tension headaches, and visual hallucinations. Once the patient discontinued phenelzine, depression returned with no other signs and symptoms. It was suggested that the patient experienced a pharmacodynamic interaction occasioned by additive stimulant activities of phenelzine and ginseng. Extracts of *P. ginseng* inhibits cyclic AMP phosphodiesterase enhancing psychoactive effect in combination with monoamine oxidase inhibitors such as phenelzine [28, 89]. Chronic use of ginseng on its own has been associated with manic psychosis [90]. Thus, the potential of ginseng for additive CNS effect, in addition to its metabolism-linked interaction with neuropsychiatric drugs, necessitates extreme caution in its use among patients on prescription CNS drugs.

3.5. Hydroxycut

Hydroxycut is a popular herbal formulation marketed for weight loss. Initially introduced in 2002, hydroxycut formulations have undergone changes. Earlier reported CNS and cardiovascular adverse effects were attributed to the ephedra components which the FDA banned in 2004 [91]. Modified ephedra-free formulation was later popularized but hampered by reports of hepatotoxicity that prompted the issuance of a safety warning by the FDA, and subsequent withdrawal in 2009 of the product from the market by the manufacturer [92, 93]. There has been a newer formulation of hydroxycut on the market for the same indication for which adverse effects have also been reported [94, 95]. In a published report highlighting an apparent HDI with this newer hydroxycut formulaion, Cvetanovich *et al.* reported the case of a patient being treated for depression with citalopram, who developed reversible cerebral vasoconstriction syndrome (RCVS) during concurrent supplementation with hydroxycut for weight loss [29]. The herbal product was believed to have exerted an additive or synergistic sympathomimetic effect through some of its components, including caffeine (the daily dose of the hydroxycut formulation includes 400 mg of caffeine). More clinical data is required to ascertain the safety of hydroxycut used alone or with other drugs.

3.6. Kava

Commercial kava formulations are made from the extracts of the rhizome of the kava plant (*Piper methysticum).* The pharmacological activities of kava have been attributed to kavalactones, which are concentrated in the rhizomes [96]. Originally used among the pacific islanders for cultural and medicinal purposes, kava has gained popularity in Western countries for its anxiolytic and sedative effects [97]. While several studies have failed to demonstrate any significant clinical benefits of kava, others have shown that kava can be beneficial in anxiety disorders [98-101]. A recent review of several clinical studies suggests that kava is superior to placebo in reducing anxiety symptoms [102]. As the use and popularity of kava grew, there were reports of kava-associated hepatotoxicity, leading to initial restrictions in its use in some countries [103, 104]. Despite the general concern about its safety, kava is still popularly consumed for CNS benefits. There is, therefore, concern for HDIs among those who consume it concurrently with their prescribed medications.

Extracts of kava have shown strong inhibitory activities against multiple isoforms of CYP [81, 105, 106]. Interactions of kava with CNS drugs have also been demonstrated in animal studies [107, 108]. These non-clinical interactions have not always translated into clinical HDIs.

A study in 18 health volunteers did not show any clinically relevant interaction between kava and bromazepam [104]. Two case reports, however, suggested that kava use with prescription neuropsychiatric medications may not always be safe. A patient who was on pharmacotherapy with alprazolam went into a coma after kava consumption in an apparent HDI involving kava-mediated CYP inhibition leading to increased alprazolam activity [30]. The second case report was about a patient who had been stabilized on levodopa, but suddenly developed movement disorders following a concurrent intake of kava [31]. The apparent reduction in the effectiveness of levodopa could be explained by the known inhibitory effects of the kavalactones on dopaminergic transmission [109, 110]. Due to the effects of kava on the drug-metabolizing enzymes, potential hepatotoxicity, and CNS effects, it may be clinically prudent to avoid kava-drug combination, even in the absence of sufficient clinically relevant HDI studies.

3.7. Kratom

Originating from Southeast Asia, the plant *Mitragyna speciosa* is an herb traditionally used for its analgesic effect. Mitragynine, the active constituent, is a mu-opioid receptor agonist, thus, exhibiting opioid-like pain relief and has made kratom a popular product among patients with opioid use disorder. Kratom is also used as complementary medicine to manage diabetes, diarrhea, improve circulation, enhance alertness and concentration, and increase libido [111-114].

While crude extracts of kratom have shown inhibitory and inductive activity against multiple CYP isozymes, mitragynine itself is a substrate and inhibitor of CYPs [115–117].

One case report of an HDI with mitragynine involved a concurrent use with quetiapine, a CYP3A4 substrate. The 27-year-old man with a history of Asperger Syndrome, bipolar disorder, and substance use disorder was found deceased in his residence with a lethal blood concentration of quetiapine (12 mg/mL) in conjunction with a qualitative presence of mitragynine [32]. The fatality was attributed to quetiapine accumulation as a result of mitragynine-mediated inhibition of CYP and P-gp. CYP inhibition reduces the

systemic clearance of quetiapine, while the inhibition of intestinal P-gp enhances the absorption and bioavailability of quetiapine. The potential for deleterious HDIs with kratom is very significant considering its use among patients with CNS disorders, its tendency to be abused, and its effects on DMEs. It is advisable to avoid concurrent use of kratom and CNS drugs.

3.8. Noni (*Morinda citrifolia*)

Extracts and formulations of *Morinda citrifolia* have been used as nutritional and medicinal supplements for over 2000 years [118]. It has been reported to contain several phytochemicals including scopoletin, octoanoic acid, terpenoids, alkaloids, and anthraquinones. Its extracts are traditionally used for the treatment of, among others, infections, cardiovascular and neuropsychiatric disorders [119]. Noni juice, made from fruits, is one of the most popular products of *M. citrifolia*. Extracts of noni have been shown to modulate the metabolic activities of multiple CYP isoforms. [120, 121]. In a published report, Kang *et al.* reported the case of a patient whose epilepsy has been managed with phenytoin for over 10 years without major side effects [33]. The patient developed poor seizure control after repeated consumption of noni juice. Noni juice had been earlier reported to reduce the AUC of phenytoin in rats through apparent induction of the CYP2C9-mediated phenytoin metabolism [122]. Thus, in the current patient, the concomitant use of noni juice resulted in the subtherapeutic exposure to phenytoin resulting in seizure. This represents a typical PK HDI that should be avoided in patients taking drugs that are metabolized by CYPs.

3.9. Piperine

Piperine is the major bioactive phytochemical in black pepper (*Piper nigrum*) and other *Piper* species. Piperine-rich extracts are often marketed as medicinal supplements for use in enhancing attention and cognition. Some studies have suggested beneficial effects in vitiligo and cardiovascular diseases [123, 124]. Preclinical studies have shown the inhibitory effect of piperine on metabolic enzymes and transport proteins [125]. As such, it has been touted as a potential pharmacokinetic enhancer capable of influencing the oral bioavailability of neuropsychiatric drugs. In a placebo-controlled clinical study conducted in 24 healthy individuals, pretreatment with piperine caused a statistically significant increase in the half-life and decrease in the clearance of midazolam [34]. However, no significant difference was observed in the $AUC_{0\text{-}5h}$ between the piperine and the placebo group.

In two studies in patients with epilepsy, authors compared the steady-state PK of phenytoin and carbamazepine before and after a single piperine dose administration [35, 36]. In both cases, piperine increased the AUC and the steady-state concentration of the drugs while decreasing their clearance. For supplements like piperine, concurrent use with drugs like phenytoin and carbamazepine, which have a narrow margin of safety, should be discouraged. The use to enhance oral bioavailability has not been validated. However, when such use is employed, deliberate efforts for therapeutic drug monitoring should be utilized to established optimal dosing parameters.

3.10. Rhodiola

Rhodiola rosea, also known as roseroot or golden root, and originally found within the provinces of Iceland, Norway, Sweden, and Russia, is a herbal product used as complementary medicine for increasing endurance and work performance and to manage fatigue, impotence, fatigue, anxiety, stress, mood disorders, cancer, and tuberculosis [126, 127]. Laboratory studies have shown that roseroot is capable of neuronal stimulation to enhance the activity of neurotransmitters - noradrenaline, dopamine, serotonin, and acetylcholine, resulting in pronounced psychotropic effects [128-131]. It has been investigated in human clinical studies showing promising results in generalized anxiety disorders, depression, stress, fatigue, and exercise endurance [132-136]. Extracts of roseroot have been found to potently inhibit CYP3A4, CYP2D6, and P-gp, which is significant for CNS drugs [137, 138]. Extracts of rosewood also inhibited the CYP2C9-dependent metabolic pathway in a clinical study, which may be significant for neuropsychiatric drugs that are CYP2C9 substrates [139].

In a published case report, a patient with recurrent depression treated with paroxetine developed serotonergic syndrome after self-medicating with rhodiola [37]. The 68-year-old had been stable on paroxetine before initiating supplementation with roseroot to 'strengthen nerves'. The development of symptoms consistent with serotonin syndrome - reduced concentration, irritability, restlessness, excessive sweating, loss of appetite and insomnia - was thought to be induced by multiple mechanisms, including the serotonergic effect of roseroot and the potentiation of paroxetine effect by roseroot-mediated CYP2D6 inhibition and reduced paroxetine clearance. Thus, the intrinsic CNS effects of roseroot and its inhibitory effect on CYPs make it an herbal candidate to induce pharmacodynamic and pharmacokinetic interactions with neuropsychiatric drugs.

3.11. St John's Wort

SJW (*Hypericum perforatum)* is a well-known herbal product used for the management of mild to moderate depression, an indication for which it has been widely investigated with positive clinical benefits [140]. The global popularity of SJW was likely enhanced by its inclusion in official recommendations for the treatment of depression [141]. Other traditional indications for SJW include somatoform disorders, premenstrual syndrome, and alcohol withdrawal [142-144]. Several constituents have been isolated and characterized from SJW, with hyperforin identified as the antidepressant entity capable of centrally inhibiting the synaptic reuptake of serotonin, dopamine, and norepinephrine [145].

SJW is notorious for its inductive effect on CYPs and P-gp, with consequential HDI with several drugs, including immunosuppressants, protease inhibitors, tricyclic antidepressants, antihistamines, and hormonal contraceptives [38, 39, 146-148]. There is an abundance of clinical evidence in the literature to show clinically significant HDIs between SJW and most CYP/ P-gp substrates. Apart from CYP/P-gp induction, SJW mediates interactions through its serotonergic effects.

Three clinical studies, three case ports, and one case series highlight the evidence of clinical interactions between

SJW and neuropsychiatric drugs (Table **1**). Following well established *in vitro* results, Dresser *et al.* investigated the ability of SJW to interact with CYP3A4 in a 2-way, open-label crossover study of 21 healthy subjects using midazolam as the probe substrate. Pretreatment with SJW was associated with a 2.7-fold increase in the oral clearance, 50% reduction in C_{max}, and a 44% reduction in the half-life of midazolam [42].

The other two clinical studies were performed in an open-label crossover design where the steady state pharmacokinetics of amitriptyline and alprazolam were compared pre- and post-SJW treatment. Pretreatment with SJW caused a statistically significant increase in the clearance and decrease in the AUC and half-life of both alprazolam and amitryptyline (Table **1**) [38, 39]. These findings were anticipated because alprazolam, like most other benzodiazepines, and amitriptyline are substrates of CYPs, which are potently induced by SJW.

In what may likely be due to induction of clozapine clearance by SJW, a published case report documented a patient with a history of schizophrenia stably managed by clozapine and who began to experience symptoms after initiating SJW supplements [41]. The discontinuation of SJW resulted in normalized clozapine levels and controlled symptoms.

A typical pharmacodynamic interaction with SJW was also reported in a patient who had been on SJW for several years and then developed orofacial dystonia following the concurrent use of bupropion [40]. The combination was believed to exert additive inhibition of serotonin reuptake, with additional enhanced dopaminergic effects such as dystonia. A similar effect has been reported in a patient with chronic depression whose concurrent use of paroxetine and SJW resulted in symptoms consistent with serotonin syndrome - incoherence, nausea, weakness, fatigue, and limp muscle tone [43]. Lastly, Lantz *et al.* reported 5 patient cases with depression/anxiety treated with sertraline or nefazodone [44]. After initiating supplementation with SJW, each patient experienced signs and symptoms of serotonin syndrome within 2-4 days. Discontinuation of the combination resolved the symptoms in all the patients.

HDIs with SJW can be one of the most significant in neuropsychiatry due to the popularity of SJW among patients with depression and other CNS disorders. The interactions are mechanistically predictable and dangerous. On one hand, there is risk of therapeutic failure due to SJW-mediated enhanced clearance of neuropsychiatric drugs. On the other hand, additive or synergistic effects of SJW on the central neurotransmitters have consequential psychotropic effects. Concomitant administration should be avoided in patients taking prescription drugs for neuropsychiatric disorders.

3.12. Terminalia and Commiphora Ayurvedic Mixtures

Terminalia chebula (myrobalan) of the Combretaceae family and species of *Commiphora* (frankincense- and myrrh-rich family of Burseraceae) are two common herbal components of Ayurvedic mixtures. *T. chebula* is a well-known herbal product in India and Middle Eastern countries for the treatment of dementia, diabetes, digestive and urinary tract diseases [149]. It is claimed to help improve memory retention and cognition, making it a commonly used herbal supplement in patients with psychological and psychiatric disorders, including confusion, depression, Alzheimer's disease, general apathy, and misanthropy [150]. The pharmacologically active compounds of *T. chebula* are polyphenols (tannins) which are expressed in the sour but edible fruits [151].

Herbal products from the *Commiphora* species are commonly used in Asia to treat inflammatory diseases, cardiovascular disorders, trauma, arthritis, and obesity [152]. Phytosteroidal compounds found in the resinous exudates are believed to be responsible for the pharmacological effects of Commiphora [153, 154]. Extracts of *T. chebula* and *C. wightii* have demonstrated inhibitory activity against CYP enzymes [155, 156].

The lone published clinical report regarding these two herbal products involved a patient with chronic depression who had combined sertraline and Ayurvedic preparations [46]. The patient soon developed acute symptoms of depression which were resolved by discontinuing the herbal remedy. The interaction was understood to result from increased clearance of sertraline due to CYP induction. Since Ayurvedic preparations are often made with multiple herbal components, the potential for deleterious HDIs is high with drug substrates of CYP. Therefore, it is safer to discourage the combination of such herbal products and neuropsychiatric products.

3.13. Valerian

Valerian (*Valeriana officinalis*) from the honeysuckle family Caprifoliaceae, is the most popular herbal supplement to enhance sleep and decrease restlessness. Valerian extracts contain several phytoconstituents, but the pharmacological property of the herb is attributed to valerenic acid and its derivatives. Valerenic acid is a partial agonist of the 5-HT receptor *in vitro* [157]. Thus, it potentially alters a variety of physiological and behavioral processes with synergic activity with other components. Valerian extracts reduce CYP3A4 and P-gp activity in both *in vitro* and animal studies [158, 159].

In a clinical trial with twelve healthy volunteers, alprazolam and dextromethorphan (probe substrates of CYP3A4 and CYP2D6, respectively) were administered to the volunteers before and after a 14-day pretreatment with valerian. The C_{max} of alprazolam was significantly increased, with no remarkable changes to any other pharmacokinetic parameters [47]. While significant HDIs were not observed in this study, the dose and duration of use may limit the conclusions.

Also, the pharmacodynamic actions of valerian in the CNS may be antagonistic or additive to the effect of prescribed neuropsychiatric drugs. In a case report of a patient who has been taking lorazepam for generalized anxiety disorder, the concomitant use of valerian/passiflora herbal preparations for 4 days resulted in the development of movement disorders [48]. This observation was attributed to the additive or synergistic CNS effect of lorazepam and valerian/passiflora, a pharmacodynamic HDI. In general, herbal products with CNS effect may not only elicit PK HDI but sometimes can precipitate antagonistic, additive, or synergistic central drug effects.

Table 2. Neuropsychiatric drugs that are substrates to cytochrome P450 enzymes and P-glycoprotein.

Enzyme/Transporter	Substrates
CYP1A2	Carbamazepine, Chlorpromazine, clomipramine, clozapine, duloxetine, fluvoxamine, loxapine, mirtazapine, olanzapine, perphenazine, thioridazine, thiothixene, trifluoperazine.
CYP2B6	Bupropion, sertraline.
CYP2C9	Phenobarbital, phenytoin, primidone, valproic acid.
CYP2C19	Amitriptyline, clobazam, diazepam, clomipramine, citalopram, escitalopram, phenobarbital, valproic acid.
CYP2D6	Amitriptyline, aripiprazole, chlorpromazine clozapine codeine, fluoxetine, fluphenazine, haloperidol iloperidone mirtazapine, olanzapine paroxetine, perphenazine risperidone thioridazine, tramadol, vortioxetine.
CYP2E1	Ethosuximide, felbamate, phenobarbital, primidone.
CYP3A4	Amitriptyline, Aripiprazole Haloperidol carbamazepine, clobazam, clonazepam, clozapine, diazepam, ethosuximide, felbamate, iloperidone loxapine lurasidone pimozide quetiapine risperidone tiagabine, ziprasidone, zonisamide.
UGTs	Lamotrigine, valproic acid.

4. DISCUSSION

Some of the top-selling herbal products, including SJW, kava, ginkgo, and valerian, are traditionally used for the prevention and treatment of neuropsychiatric disorders. Due to the laxed regulatory requirement for marketing herbal products, not much premarketing information regarding efficacy and safety is available for these herbs. This has placed the responsibility of identifying and managing safety-related concerns of herbal medicines on clinicians, most of whose training did not involve herbal medicine. Unprompted, most patients do not disclose their use of herbal medicines to their health professionals. This often complicates therapy and delays the identification and treatment of herbal-related side effects or HDIs.

Although controlled clinical studies on HDIs are very sparse in literature, there is a preponderance of information on the ability of herbal products to cause pharmacokinetic and/or pharmacodynamic drug interactions. Ascertaining the specific mechanism or the actual interacting phytochemical in a herbal product is challenging. This is because many marketed herbal products are made of mixtures of different herbal species and/or dietary supplements whose biological disposition in humans is poorly understood. Pharmacokinetic interactions can be gastrointestinal, in which case the presence of the herbal product influences the absorption or action of the drug within the gastrointestinal tract. This is important because the vast majority of herbal products are orally administered. CYP3A4 and P-gp are richly expressed in the human small intestinal enterocytes. The modulatory activities of herbal products on these enzymes and transporters are known to alter the oral bioavailability of their substrates. Absorbed herbal products can elicit further pharmacokinetic interactions through the modulatory actions on the hepatic enzymes, other tissues enzymes, transport proteins (including the efflux and uptake proteins), plasma/tissue binding proteins, as well as renal excretory pathways [160].

The inhibition of DMEs and transport proteins often leads to delayed and/decreased systemic clearance of drugs. The resulting drug accumulation from DME inhibition can precipitate toxic manifestations. When DMEs are induced, metabolism is enhanced with the risk of subtherapeutic exposure to the prescribed drugs. Drug transporters, including P-gp, are part of the physiologic blood-brain barrier regulating CNS exposure to drugs. Therefore, alterations in the functions of the transport proteins present a real risk to central functions due to enhanced/reduced drug access. Several neuropsychiatric drugs, including tricyclic antidepressants, antiepileptic drugs, antipsychotics, benzodiazepines, and narcotic analgesic agents, are substrates of CYPs and P-gp (Table **2**). Healthcare providers can thus be proactive in the anticipatory prevention of HDIs with these drugs.

Pharmacokinetic HDIs can also occur through the influence of herbal products on the glomerular filtration or tubular reabsorption in the kidneys. This mechanism should be of concern with herbal products with known nephrotoxicity.

Of particular importance is pharmacodynamic HDIs in neuropsychiatry. The beneficial effects of most herbal medicines in mental health have been attributed to central receptor activity and/or interactions with central neurotransmitters. The mu receptor-stimulating effect of kratom or the serotonin reuptake inhibitory activity of hyperforin in SJW are examples of mechanistic pathways through which herbal products can exert additive/antagonistic pharmacodynamic HDIs.

This review identified 13 herbal products - celery, echinacea, ginkgo, ginseng, hydroxycut, kava, kratom, moringa, piperine, rhodiola, St. John's wort, terminalia/commiphora ayurvedic mixture and valerian – all of which have shown interactions with specific neuropsychiatric drugs. While the extracts of celery, ginkgo, kava, SJW, and valerian modulate the activity of DMEs, products of ginkgo, ginseng, kava, kratom, rhodiola, and SJW have direct pharmacodynamic effects on the CNS, affecting GABAnergic and/or serotonergic transmission.

Some other commonly used herbal products in neuropsychiatric conditions include Black cohosh, German chamo-

mile, evening primrose, hops, lemon balm, passion flowers, and skullcap. While there are no reported clinical interactions with these herbs, some of them have shown inhibitory/inductive effects on hepatic enzymes based on *in vitro* studies [161, 162].

The majority of the evidence of clinically relevant HDI presented in this review is based on case reports and case series. This type of clinical evidence is inferior to randomized controlled trials and other clinical studies that include larger number of human subjects. Thus, the data presented should be understood within the context and limitations of case studies/series. Inter-individual variations in pharmacokinetics and pharmacodynamics, individual-specific factors, and misdiagnosis (wrong herbal association) by clinicians are some of the limitations of HDI case studies/series.

It is vital, however, for both patients and providers alike to be educated on the potential interactions between herbal products and prescription medicines. Informed use of an herbal product can be beneficial in therapy. One of the best ways to avoid dangerous HDIs, if herbal use is necessary, is to avoid same-time coadministration, which minimizes absorption-related interaction and may also reduce the pharmacokinetic interactivity. Overall, HDIs could be serious and affect therapy outcomes in the pharmacotherapy of neuropsychiatric disorders.

CONCLUSION

Herbal products are not entirely free of adverse effects and can alter therapeutic outcomes when co-administered with prescription drugs. Healthcare professionals need to be aware of their patients' habitual/occasional use of herbal products for a myriad of indications. In order to prevent or mitigate the effect of HDI in neuropsychiatry, clinicians should actively seek information on herb-drug combination use among their patients and apply appropriate clinical judgement as necessary. It is strongly suggested that continuing professional education for healthcare providers should include periodic updates on clinically relevant HDIs to make up for the current gap on this subject in most health-related curricula. With only limited data available on clinical HDIs, healthcare professionals should continue to use their clinical judgment to create appropriate treatment and monitoring plans in patients with habitual and concomitant herbal intake.

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