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Herb- Drug Interactions: A Review

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Abstract

Herbal drugs are exempt from Food and Drug Administration regulations regarding efficacy and safety. Their potential of interaction with conventional prescription drugs is a matter of great concern. This paper reviews the reported herb- drug interactions among the most commonly used and top selling herbs in the U.S.

1. Introduction

For centuries, man has used plants for medicinal purposes and over the last few decades, there has been a most remarkable revival of herbal medicine. Today, as many as one third to approximately half of all drugs available in the market are derived from plants [(1)]. However, being categorized as dietary supplements; herbal drugs are exempt from Food and Drug Administration regulations regarding efficacy and safety of active ingredients [(2)].

Of grave concern with widely used herbal therapies, is their potential of interaction with conventional prescription drugs. Extensive studies have shown that herb-drug interactions have both a pharmacokinetic and pharmacodynamic basis, most of which are attributed to the induction or inhibition of hepatic and intestinal microsomal enzymes (primarily cytochrome P450), and/or drug transporters(P-glycoprotein) [(3,4,5)]. This paper reviews the reported herb- drug interactions among the most commonly used and top selling herbs in the U.S.

Kava

Kava Kava (*Piper methysticum*) , a member of the pepper family was used for centuries as a traditional beverage in the Pacific Islands. It is consumed today for its psychoactive and pain management properties and for its muscle relaxant effects [(6)].

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However, reports of hepatotoxicity have urged countries such as Germany, Switzerland, UK, Canada and parts of Australia to impose restrictions on its sale and overconsumption. In the US, though warnings have been issued by the Center for Disease Control, the sale of Kava root and its extract still remains legal [7].

Although there is a lack of actual experimental data and a paucity of well documented evidence of the interaction of Kava kava with other drugs/herbs, clinical recommendations are based mainly on theoretical considerations. It has been postulated that the reduced effectiveness of levodopa in patients with Parkinson's disease on Kava is possibly due to its modulation of the dopamine system [8]. As stated in reviews by Pepping and Bilia *et al* , given the sedative effect of Kava , it has been hypothesized that it most likely potentiated the effects of CNS-depressants like benzodiazepines, barbiturates, anesthetic agents, alcohol and anticonvulsants [9, 10]. Interactions between Kava and anticoagulants like warfarin and phenprocoumon or antiplatelet medications like aspirin and dipyridamole have been suggested following an *in vitro* experiment conducted by Gleitz *et al*. which detected dose-dependent antithrombotic actions of (±)-kavain on human platelets [11]. Further, an *in vitro* experiment conducted by Uebelhack *et al*. suggests that kavalactones , the active constituents of Kava may theoretically display additive effects with some anti parkinson's drugs namely, MAO-B inhibitors like selegiline [12]. Kava has also been found to increase the likelihood of liver and kidney damage when used with acetaminophen , though the mechanism remains unknown [2].

Echinacea

Also called the 'purple coneflower', *Echinacea purpurea*, with its immunomodulatory properties is commonly used in the prevention and treatment of URTIs. Although no studies have been conducted to evaluate the safety or effectiveness of echinacea, in theory, immunosuppressive drugs are suggested to be affected by this herb, causing leukopenia with long-term use. Hence, this drug is not recommended for use in immunocompromised patients, such as transplant patients or those with human immunodeficiency virus (HIV) or cancer[13]. Prolonged use of echinacea has been found to result in hepatotoxicity; hence, concomitant use with other hepatotoxic drugs is best avoided [14] .

Gingko

Known for its antioxidant and neuroprotective effects, the leaf extract of the commonly used herb, *Ginkgo biloba* is used for the treatment of a variety of conditions today, which include asthma, bronchitis, tinnitus, Alzheimer's disease and other dementias, decreased memory, sexual dysfunction and multiple sclerosis [15]. Unfortunately, this herb is reported to interact with many prescription drugs. When used with anticoagulants (warfarin) and NSAIDs (aspirin, ibuprofen), ginkgo displays additive/synergistic antiplatelet and anticoagulant properties [16].

By virtue of its inductive effect on hepatic enzyme CYP2C19, it has also been found to decrease blood levels of proton pump inhibitors such as omeprazole thereby reducing their therapeutic effect [17]. Ginkgo is avoided with drugs that lower seizure threshold as it is likely to precipitate tonic clonic seizures. This herb has also been found to interact with other CNS agents such as trazodone and haloperidol by increasing the risk of sedation with the former and increasing the effectiveness of the latter.

By scavenging the free radicals produced by hypodopaminergic activity , ginkgo also decreases the extra pyramidal side effects of haloperidol [18]. Studies conducted by Yoshioka *et al* suggest that the concomitant oral use of *Ginkgo biloba* leaf extract with oral nifedipine reduces its first-pass elimination thereby increasing this calcium channel blocker's plasma concentration and possible adverse effects. This action is possibly due to its inhibitory activity on CYP 3A4 [19].

Ginseng:

Native to East Asia, Ginseng is obtained from the aromatic root of a plant of the genus *Panax* [20] . Ginseng is widely used today to improve the immune system, cognition, several aspects of fatigue, appetite, physical performance, anemia, glucose regulation, digestion, sexual performance, and to decrease stress. This drug is also being reported for its use in cancer treatment, particularly breast and colorectal cancer [21]. Studies suggest that ginseng can induce a moderate estrogen-like effect on women such as vaginal or uterine bleeding and mastalgia [22].

Coon J *et al* have reported that ginseng was found to interact with most antidepressants of the monoaminoxidase inhibitor class (Isocarboxazid,Tranylcypromine, phenelzine) causing an increased risk of occurrence of CNS effects such as manic like symptoms, headache,insomnia and tremulousness [23]. Studies by Yuan CS *et al* showed that the action of ginseng on the enzyme CYP2C9 decreased the effectiveness of warfarin and other anticoagulants, thereby predisposing patients to thrombotic events.[24] Although the mechanism remains unknown, ginseng has also been found to decrease the efficacy of diuretics such as Ethacrynic acid, Furosemide and Torsemide thereby making patients susceptible to fluid overload and heart failure consequently [25]. Further, by inhibition of CYP3A4, ginseng also interacts with cardiovascular agents such as digoxin and nifedipine leading to elevated plasma levels of these prescription drugs and an increased risk of adverse effects [26].

Garlic

Allium sativum, better known as garlic is one of the best selling herbal remedies today and is also used as a food/spice [27]. This herb contains numerous volatile sulfur compounds such as alliin, allicin, diallyl disulfide, ajoene etc. to which its antibacterial, antiviral, antifungal, ntihypertensive, blood glucose lowering, antithrombotic, antimutagenic and antiplatelet actions may be attributed [28 , 29]. However, like most other herbal drugs, garlic too is found to interact with a variety of prescription drugs. It displays complex cardiovascular effects including antiplatelet activity and hence enhances the pharmacological effects of anticoagulant and antiplatelet drugs [30]. It has also been found to have a synergistic/additive effect with antidiabetic medications such as chlorpropamids resulting in a fall in blood glucose levels. Studies have also shown that garlic may reduce the efficacy of anti- AIDS drugs such as saquinavir [31].
Gwilt *et. al* studied the effect of garlic on the metabolism of acetaminophen in man and suggested that the prolonged use of this herb could alter the pharmacokinetics of this OTC drug [32].

The compound allicin in garlic has been found to induce the enzyme CYP3A4. This may result in clinically important decreases in concentrations of drugs metabolized by this enzyme which include protease inhibitors, cyclosporine, ketoconazole, itraconazole, glucocorticoids, oral contraceptives, verapamil, diltiazem, lovastatin, simvastatin, and atorvastatin [33] .

St. John's Wort

St John's wort, from *Hypericum perforatum* is a perennial herb with bright yellow flowers, native to West Asia, Europe and North Africa. The herb is used to treat a variety of conditions ranging from moderate to severe depression, premenstrual syndrome, anxiety and rarely some cases of obsessive compulsive disorder. Unfortunately, this herbal drug has been found to interact with a number of prescription drugs used today.

Induction of CYP3A4 by co-administration with St. John's wort has proven to decrease the bioavailability of immunosuppresants cyclosporin and tacrolimus significantly leading to transplant rejection and life threatening risks to the patient. Concomitant use of SSRIs ,such as sertraline with St.John's wort has been observed to inhibit the reuptake of neurotransmitters, thereby resulting in serotonin syndrome in a few cases [(34)]. Anti HIV drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors are extensively metabolised by CYP3A4, which when stimulated by simultaneous use of St. John's wort leads to a reduction in plasma drug concentrations and treatment failure [(35).]

Although the underlying mechanism still remains ambiguous, well documented clinical studies reveal that significant interactions of St. John's wort with anticoagulants like warfarin and phenprocoumon can occur, resulting in decreased therapeutic activity [(36).] Results of interaction studies conducted by Hall SD *et al* and Pfunder A *et al* together with several frequent reports of irregular bleeding to drug authorities, suggest that the co-administration of St. John's wort with progestogen containing oral contraceptive pills decreases the bioavailabilty of the latter. This has been postulated to be due to the induction of CYP3A4 by St. John's wort which then speeds up the metabolism of these drugs [(37, 38)].

By a similar mechanism, this herbal drug has also been found to significantly reduce the therapeutic efficacy of tricyclic antidepressants such as amitryptiline , nortryptiline etc (34).Nebel A *et al* reported a case of reduced plasma concentrations of theophylline in a patient due to co-administration of St. John's wort . This was suggested to be due to the induction of the metabolizing enzyme CYP3A4 [(39).]

Mueller *et al* postulated that co-medication of patients on digoxin with a high dose of St. John's wort altered its pharmacokinetics resulting in a 37% reduction in peak plasma concentrations of digoxin [(40)]. While studying the interaction between St. John's wort and atorvastatin in patients with hyperlipidemia, Andren *et al* reported that administration of St. John's wort resulted in significant increases in serum total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations in recipients versus controls, thereby suggesting that this herb reduced the therapeutic efficacy of statins [(41)]. Various therapeutic drugs such as digoxin, theophylline, cyclosporine, tacrolimus, tricyclic antidepressants, warfarin, and protease inhibitors interact with St John's wort to display significantly reduced concentrations ,hence causing treatment failure[(42)].

Chamomile

Commonly found in tea and beauty aids, the chamomile plant (*Matricaria recutita*) is valued for its ability to help maintain health. Various preparations of chamomile are used to treat gastrointestinal spasms, digestive disturbances, flatulence, bloating and inflammatory diseases of the gastrointestinal tract and upper respiratory tract. This herb also promotes the healing of wounds and is commonly found in creams and lotions that treat wounds, skin irritations, bacterial infections, and diaper rash and other inflammatory skin conditions. In addition, it has anti-anxiety properties and can serve as a mild sedative to induce sleep.[43]

As the documentation of drug interactions through case reports and case studies is limited, they are based on known pharmacological properties of the plant and are mostly hypothetical [44].

Segal *et al* reported a case where a 70 year old patient on warfarin who used chamomile for an URTI was hospitalized with multiple internal hemorrhages, suggesting that the coumarin constituent in this herb increased the risk of bleeding when used with antiplatelet and anticoagulant agents [45,46].

It has also been hypothesized that owing to its sedative effects, chamomile can increase the drowsiness caused by drugs such as benzodiazepines, narcotics, alcohol, antidepressants and even herbs such as valerian and St. John's wort [44].

Milk thistle

Native to the Mediterranean region, this flowering herb, *Silybum marianum* is used extensively as a remedy for a variety of ailments such liver cirrhosis, chronic hepatitis , gall bladder disorders, hyperlipidemias and to reduce the growth of cancer cells in breast, cervical, and prostate tissues [47]. Silybum too, however, has been found to exhibit a fair share of interactions with prescription drugs. In studies on the effect of its active component silibinin on the pharmacokinetics of the anti-tuberculous drug pyrazinamide, Wu and Tsai suggested that the herb altered the hepatobiliary elimination of pyrazinamide [48].

Experiments conducted by Rajnarayana *et al*., showed that another component, silymarin caused an increased clearance of metronidazole and its metabolite hydroxymetronidazole thereby decreasing the half life of this antiprotozoal agent [49]. Mills *et al*. reported that milk thistle could cause a small to moderate induction of CYP3A4 which could bring about a minor reduction of the anti-HIV drug indinavir[50].

Valerian

Valerian , a herbal remedy derived from the dried roots of the plant, *Valeriana officinalis*, has been used for over a thousand years as a mild sedative and hypnotic. Currently, it is widely used to relieve mild cases of anxiety, insomnia, menstrual cramps and to soothe skin rashes and swollen joints. It is also used as a carminative to relieve gas in the stomach and intestines [51].

Although no evidence from clinical trials related to drug interactions with valerian exists, there are many theories regarding the same, based on its pharmacokinetic and pharmacodynamic potential and on existing case reports [52]. It has been hypothesised that Valerian can potentiate the sedative effects of drugs such as barbiturates, benzodiazepines and alcohol mediated via the neurotransmitter gamma-aminobutyric acid [53] .

Corte *et al* have reported that concurrent use of haloperidol with valerian led to an increase in lipid peroxidation levels in hepatic tissue , suggesting adverse interactions between haloperidol and this herbal drug (54) .It has also been postulated that Valerian demonstrates CYP3A4 inhibition and hence interacts with CYP3A4 substrates such as atorvastatin and warfarin [52].

Saw palmetto

Serenoa repens , commonly known as the Saw palmetto is a dwarf palm tree that grows in Texas, Florida, Georgia, and southern South Carolina. It is one of the most widely used herbal drugs for the treatment of lower urinary tract symptoms (LUTS) and for benign prostatic hyperplasia (BPH) [55]. As this drug displays estrogenic, anti-androgenic and anti-progesterone properties, it is considered best to avoid its concomitant use with other hormonal therapies (eg, Finasteride, birth control pills, hormone replacement therapy, flutamide), which could affect the level of sex hormones [56, 57].

Use of saw palmetto with NSAIDs/anticoagulants is contraindicated because of its ability to inhibit the enzymes cycloxygenase and 5- lipoxygenase as it may predispose to serious bleeding.

Although the mechanism of interaction remains unknown, concurrent use of this herb with drugs such as disulfiram and metronidazole has been shown to cause excessive nausea/vomiting[58].

2. Conclusion

With sales reaching over $5 billion in 2007 in the United States alone, herbal dietary supplements have gained utmost importance (59) and its use, by a sizeable number of the world population can no longer be ignored . Though a matter of grave concern, its potential to interact with prescription medicines, remains an understudied field of research. There is a dire need for more information viz, preclinical, animal studies, premarketing and postmarketing surveillance in order to guarantee the safety of herbal medicines in patients.

It is imperative that health care professionals, suppliers ,consumers and regulatory authorities be aware of the possible side effects and interactions of these herbs when co-administered with conventional drugs [60]. Further with many more herb-drug interactions being reported and discovered, it becomes increasingly necessary for physicians to explore herbal usage with their patients and to provide cautions. Patients should be educated that the FDA does not regulate herbal medications and hence the safety of herbal preparations is not assured. Collaborating with a pharmacist would help to avoid potential herb-drug interactions in patients .

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