An Insight into Herb - Drug Interactions

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ABSTRACT: Alternative medicine is becoming popular worldwide and this is clearly evident from the rapidly escalating sales figures. The time tested and clinically proven herbal medicines like St. John’s wort, Ginkgo biloba, Garlic, Ephedra, Echinacea etc., make up most of the world’s market as far as alternative medicine is concerned. In spite of its increasing popularity, global criticism regarding the safety of herbal medicines is gaining importance. The surfacing of the adverse effects/adverse events due to concomitant use of herbs and prescription medicines undermine the safety of herbal medicines. The safety of herbal medicines still remains a daunting task. The herbs like St. John’s wort, Ginkgo biloba, Garlic, Ephedra, Echinacea etc., have been reported to interact pharmacokinetically and pharmacodynamically with several prescription medicines. The available literature also bolsters that concomitant use of herbs and drugs can lead to several adverse effects/adverse events. This article presents most of the significant herb – drug interactions reported till date along with a note on the predicted interactions which may/may not occur. There are certain herb – drug combinations which can produce therapeutic benefit and these beneficial herb – drug combinations are also detailed in this article. This review gives an insight into herb – drug interactions, stressing the need to carryout studies on herb – drug interactions at a faster pace, which can strengthen the concept of herbal medicine.

KEYWORDS: Herbal medicine; herb – drug interactions; St. John’s wort; CYP enzymes; predicted interactions; safe combinations

Introduction

Advances in western medicine have dramatically increased health conditions and life expectancy of people. In spite of the latest developments in allopathic system of medicine people still seek alternative and complimentary system. The use of herbal medicine to treat a wide range of conditions is rising rapidly, leading to increased intake of phytochemicals. Recent studies reveal potential fatal interactions between herbal medicines and drugs. Herbal medicine is amongst the 16 alternative systems of medicine, which is used to treat existing illnesses and also for preventive and health maintenance purposes (Ioannides, 2002). Herbs like St. John’s wort, Ginkgo biloba, Feverfew, Ginger and Kava, Chamomile, Echinacea, Saw palmetto, Silymarin make most of the worlds market (Blumenthal, 1999). The increasing popularity of alternative therapies, including herbal remedies is a new challenge for health care providers because the evidence on safety of herbal remedies is incomplete, complex and confusing. The herbal medicines are certainly associated with risks and benefits (Ernst, 2003). Interactions between herbal medicines and drugs are based on the same pharmacokinetic and pharmacodynamic principles as drug – drug interactions. Clinically important interactions appear to involve effects on drug metabolism via cytochrome P-450 isoenzymes, impairment of hepatic or renal function, and other possible mechanisms (Dresser et al., 2000; Evans, 2000).

The present review gives an insight into herb – drug interactions, clearly focusing the need to understand and also to assess the safety of herbal medicine. The content of the article is detailed from the therapeutic point of view of the herbs. Based on the possibility of co – administration herbs are classified into three categories i.e., category I – herbs having higher possibility of co – administration with drugs; category II – herbs having moderate possibility of co – administration with drugs and category III – herbs having less possibility of co – administration with drugs. This review also enlightens about the herbs which may/may not have inherent potential to interact with the drugs based on evidences of in – vitro studies, along with specific emphasis on the benefits of certain herb drug combinations.

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Interactions between Immunomodulatory Herbs – Drugs

The present day tech savvy world is beauty and health conscious and one of the popular uses of herbal medicine is to enhance immune system (Foti and Wholstrom, 2008). The global promotion of herbal products/herbal medicines as immune boosters is on the rise. Immunomodulation using herbs are always chosen as a better alternative to specific diseases, when the inherent defense of a person has to be activated under the conditions of impaired immune response (Atal et al., 1986). Ginseng is one of the highly commercialized immunomodulatory herbs, which is very common in most of the retail stores. Ginseng is purported to strengthen normal body functions increase resistance to stress and improve sexual function (Ellis and Reddy 2002). Ginseng is known to interact pharmacodynamically and pharmacokinetically with several drugs (Coon and Ernst 2002). Studies reveal that it alters the pharmacokinetics of the drugs like opioid analgesics (Abebe et al., 2002), bumetanide, ethacrynic acid, furosemide/torsemide, digoxin, amloidipine (Coon and Ernst, 2002). A pharmacodynamic interaction between P. ginseng and phenelzine is known to produce adverse effects like headache, tremulousness, manic episodes but the actual mechanism for this interaction is unknown (Jones and Runikis, 1987). Clinical studies on healthy volunteers reveal that ginseng and warfarin combination decreases the international normalized ratio (INR) values leading to increased risk of bleeding (Janetzky and Morreale, 1997) and it is bolstered by several studies (Jiang et al., 2004). Another immunomodulatory herb of choice is Echinacea, which is used as non-specific immunostimulant for upper respiratory tract infections. Echinacea is known to interact with drugs like itraconazole, fexofenadine and lovastatin (Budzinski, 2000). The active constituents of Echinacea are proven to be hepatotoxic and there is a possibility for potentiation of hepatotoxicity when it is co – administered with acetaminophen or other NSAIDs (Abebe et al., 2002). The immunomodulatory potential of Echinacea can lead to loss of activity of immunosuppressant drugs on concomitant usage (Daniel et al., 2006). The interaction potential of the other immunomodulatory herbs with the prescription drugs is listed in the Table 1.

Table 1. Interactions between Immunomodulatory herbs and drugs.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Drug/Class of drugs</th>
<th>Possibility of co – administration</th>
<th>Mechanism/Outcome of Herb – Drug Interaction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astragalus (ASTRAGALUS MEMBRANACEUS)</td>
<td>Azathioprine Cyclosporine Methotrexate</td>
<td>III Antagonism</td>
<td>Zhou et al., 1982</td>
<td></td>
</tr>
<tr>
<td>Borage (BORAGO OFFICINALIS)</td>
<td>Hypnotics</td>
<td>II Potentiation</td>
<td>Miller, 1998</td>
<td></td>
</tr>
<tr>
<td>Echinacea (ECHINACEA PURPUREA)</td>
<td>Acetaminophen</td>
<td>II Potentiation of Hepatotoxicity</td>
<td>Abebe et al., 2002</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids Cyclosporine</td>
<td></td>
<td>III Antagonism</td>
<td>Miller, 1998</td>
<td></td>
</tr>
<tr>
<td>Fexofenadine Itraconazole Lovastatin</td>
<td></td>
<td>III Inhibition of CYP3A4 leading to increase in drug concentration</td>
<td>Budzinski et al., 2006</td>
<td></td>
</tr>
<tr>
<td>Ginseng (PANAX GINSENG)</td>
<td>Amlodipine</td>
<td>I Induction of CYP3A4</td>
<td>Dergal et al., 2002</td>
<td></td>
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<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td>McRae et al., 1996; Dasgupta et al., 2003</td>
<td></td>
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<tr>
<td>Hexobarbital</td>
<td></td>
<td>II Induction of CYP2C9</td>
<td>Knedel et al., 1988</td>
<td></td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td></td>
<td>III Decreased activity of opioids – clear mechanism is unknown</td>
<td>Takahashi and Tokuyama, 1998</td>
<td></td>
</tr>
<tr>
<td>Phenelzine and MAD inhibitors</td>
<td></td>
<td>I Increased CNS side effects due to additive effect</td>
<td>Jones et al., 1987</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>II Alteration of INR value</td>
<td>Cheng, 2000; Morreale, 1997; Jang et al., 2004</td>
<td></td>
</tr>
<tr>
<td>Shankpushpi (CONVOLVULUS PLURICAULIS)</td>
<td>Phenytoin</td>
<td>I Decreased therapeutic effect</td>
<td>Dandekar et al., 1992</td>
<td></td>
</tr>
</tbody>
</table>

I – herbs having higher possibility of co – administration with drugs; II – herbs having moderate possibility of co – administration with drugs; III – herbs having less possibility of co – administration with drugs.
Interactions between Herbs used for Cardiovascular Disorders and Drugs

The herbal alternatives in cardiovascular risk group provide an additional benefit to the heart. It is with this credence that the herbs are used by cardiovascular risk group. It is revealed that 20% of the patients with acute coronary syndromes take herbal remedies for cardiac—specific purposes (Baracco et al., 2005). The herbs like Allium sativum, Berberis aristata, Commiphora mukul, Rauwolfia serpentina, Stephania tetrandra, Ligusticum wallichii, Uncaria rhynchophylla, Veratrum album, Crataegus monogyna, Allium sativum, Rosmarinus officinalis, Aesculus hippocastanum, Ruscus aculeatus are widely used cardiovascular herbs (William et al., 2004).

The herb — drug combinations in the cardiovascular risk group should be monitored very cautiously because failure to monitor such combinations can lead to life threatening events. Among these herbs garlic, guggul and hawthorn are reported to interact with drugs. The medicinal value of garlic has been accredited for more than 500 years. Garlic (Allium sativum) is used traditionally to treat infections, both orally and topically, promote wound healing and prevent cold and influenza (Harunobu et al., 2001). Modern use of garlic focuses on hyperlipidaemia, antihypertensive, antithrombotic and fibrinolytic effects, additive effect with anticoagulants, and it is believed to act for skin diseases (Mester et al., 1989). It may produce an inhibition of P- glycoprotein (P-gP) (Piscitelli et al., 2000) leading to graft rejection. In contrast to the above report it doesn’t alter the pharmacokinetics of another immunosuppressant drug i.e., mycophenolate mofetil. This variation is attributed to involvement of hepatic enzymes in the metabolism of simvastatin and cyclosporine, while it is not so in case of pravastatin and mycophenolate mofetil.

Interactions between Herbs used for Central Nervous System Disorders and Drugs

The modern world is more prone to central nervous system (CNS) disorders. Statistics warn that the incidences of stress, depression, anxiety, mania and Alzheimer’s disease are on alarming rise. According to the survey of Eisenberg et al., (1998) two of the top five conditions for which consumers choose alternative treatment are anxiety and depression. Depression and anxiety are prominent indications for herbal medicines (Roy-Byrne et al., 2005) and the majority of people with depression try complementary medicines (Silvers et al., 2006). A systematic review of the published literature reveal that Ginkgo biloba, Lavandula angustifolia, Hypericum perforatum, Valeriana officinalis, Crataegus oxyacantha, Eschscholzia californica, Matricaria recutita, Melissa officinalis, Passiflora incarnata and Piper methysticum are the commonly used herbs for CNS disorders. Among these, the use of herbal remedies like Hypericum perforatum (St John’s wort) for mild to moderate depression, Piper methysticum (kava) for anxiety and Ginkgo biloba for cerebrovascular disorders are supported by sound evidences.

St.John’s wort is a major herb of concern in herb – drug interactions due to its diverse pharmacological actions and unique potential to interact with vast majority of prescription drugs and OTC drugs like oral contraceptives. There are several studies, case reports and predictions about St. John’s wort potential to alter the pharmacokinetics of drugs. It is reported to increase significantly the Cmax and AUC of the drugs such as fexofenadine, olanzapine and decrease the Cmax/AUC of drugs. It is reported to increase theophylline and oral contraceptives. The actual mechanisms and possibilities for the above mentioned St.John’s wort mediated interactions are elaborated in Table 2. Of note, activation of CYP3A4 by St.John’s wort interaction with oral contraceptives leading to failure of contraception, decreases in the AUC of tacrolimus and leading to increased risk of organ rejection are of primary significance (Bolley et al., 2002). An interesting study about St. John’s wort reveals variation in the metabolism of drugs belonging to same class i.e., it decreases Cmax and AUC of simvastatin but not pravastatin (Sugimoto et al., 2001). Similarly it is known to alter the pharmacokinetics of cyclosporine, an immunosuppressant (Barone et al., 2000) leading to graft rejection. In contrast to the above report it doesn’t alter the pharmacokinetics of another immunosuppressant drug i.e., mycophenolate mofetil. This variation is attributed to involvement of hepatic enzymes in the metabolism of simvastatin and cyclosporine, while it is not so in case of pravastatin and mycophenolate mofetil.
Ginkgo biloba is widely touted for its potential to ameliorate the cerebrovascular complications, dementia and for memory improvement (Kleijnen and Knipschild, 1992; Turan and Martorano, 1995). G. biloba has special reference in herb - drug interactions because of the reported adverse events like intracerebral haemorrhage, subdural hematoma, and spontaneous hyphema. It is reported to interact prominently with blood thinning drugs (Chung et al., 1997), bilateral subdural hematomas (Rowin and Lewis., 1996). A single case report states that ginkgo increases the bioavailability of digoxin (Mauro et al., 2003) and other studies reveal that it decreases the bioavailability of omeprazole (Yib et al., 2004) and increases the bioavailability of diltiazem (Ohnishi et al., 2003). Pharmacodynamic alterations due to ginkgo and other drug combinations include decreased hypotensive effect of nicardipine (Shinoura et al., 2002) and decreased antihyperglycemic effect of tolbutamide (Sugiyama et al., 2004).

Kava (Piper methysticum) is widely used herbal sedative (Keller and Klohs, 1963). The major active constituents of kava are kavalactones, which are potent inhibitors of CYP3A4 (Yadhu, 2005). Kava is reported to produce an additive effect in a 54yr old patient leading to semi comatose condition who was consuming alprazolam (CYP3A4 substrate) along with kava (Almeida and Lewis., 1996). In contrast it is also reported that kava co – administration with bromazepam (Heberg, 1996). A case report of severe Parkinsonism associated with kava and L - dopa co – administration contraindicates the combinative therapy (Schelosky et al., 1995).

Sarsaparilla is also used as an immunomodulator and to treat the respiratory disorders and also as an antidepressant (Chu et al., 2006; Spielmann et al., 2006). Theoretically sarsaparilla can potentiate the hypnotic activity of the concomitantly administered hypnotic drugs. Studies reveal that sarsaparilla can lead to increased drug activity of digoxin and bismuth because the saponins present in the herb enhance the absorption of drugs (Newall et al., 1996).

The interactions of other CNS herbs with various drugs are summarized in Table 2.

**Interactions between Herbs and Drugs Acting On Blood (Blood Modifiers)**

The use of traditional medicine in combination with alternative therapy may lead to complications for patients as it is evidenced by the adverse effects of certain herbal products in patients who receive traditional anticoagulant or antiplatelet medication. Most of the blood thinners are prescribed for patients who have heart valve replacement, atrial fibrillation, congestive heart failure, or for obese persons. They may also be used for the prevention of thromboembolic disorders (Gross and Weitz 2008). The long term and in certain cases life long use of blood thinning agents is imperative in cardiovascular risk patients. In these patients the use of certain herb – drug combinations should be avoided preferably due to the possibility for the risk of bleeding. Warfarin is the common drug which is reported to interact with several herbal formulations. The warfarin – herb interactions account to the extent of the 6 – 7 % of the interaction studies reported till date (Ann, 2001). The herbs/herbal formulations containing coumarins (unica, celery, chlorella, dansheng, dong quai, chamomile, fenugreek, goldenseal, guar gum, horse chestnut seeds, papain, passionflower, red clover, sweet clover, boldo) and vitamin K (acerola, agrimony , stinging nettle, plantain) as main active constituents alter the property of blood thinning drugs either by increasing or decreasing the bleeding phenomenon by altering international normalized ratio (INR). Certain herbs like bilberry, cayenne, bromelain, capsicum, European mistletoe, feverfew, garlic are known to reduce the platelet aggregation process and increase the fibrinolytic activity (Heck et al., 2000; Patel and Gohil, 2008). In contrast to the above, the herbs such as garlic, ginkgo and saw palmetto exceptionally inhibit platelet activating factor and this mechanism is considered to be the major perpetrator for the adverse events reported with the usage of these herbs (Rosenblatt and Mindel, 1997; Cheema et al., 2001).
Table 2. Interactions between herbs used for central nervous system disorders and drugs.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Herb Indication</th>
<th>Drug/Class of drugs</th>
<th>Possibility of co-administration</th>
<th>Mechanism/Outcome of Herb Drug Interaction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areca (ARECA CATECHU)</td>
<td>Antidepressant</td>
<td>Procyclidine</td>
<td>I</td>
<td>Antagonistic effect on drug – leading to extra pyramidal syndrome</td>
<td>Deahl, 1989</td>
</tr>
<tr>
<td>Capsicum (CAPSICUM FRUTESCENCE, CAPSICUM ANNUM)</td>
<td>Circulatory stimulant, Pain reliever</td>
<td>ACE inhibitors</td>
<td>III</td>
<td>Increased risk of developing cough</td>
<td>Hakas, 1990</td>
</tr>
<tr>
<td>Chasteberry (VITEX AGNUS – CASTUS)</td>
<td>Meningeal discomforts, inhibits secretion of proactin</td>
<td>Theophylline</td>
<td>II</td>
<td>Enhanced bioavailability can lead to theophylline toxicity</td>
<td>Bouraoui et al., 1988</td>
</tr>
<tr>
<td>Feverfew (TANACETUM PARTHENIUM)</td>
<td>Arthritis, fever, Migraine headaches, digestive problems</td>
<td>Antimigraine Drugs</td>
<td>I</td>
<td>Potentiation of drug effect</td>
<td>Mulduje et al., 1982</td>
</tr>
<tr>
<td>Feverfew (TANACETUM PARTHENIUM)</td>
<td>Arthritis, fever, Migraine headaches, digestive problems</td>
<td>Warfarin</td>
<td>II</td>
<td>Additive antiplatelet effect due to inhibition of platelet aggregation</td>
<td>Heck et al., 2009</td>
</tr>
<tr>
<td>Ginkgo (GINKGO BILOBA)</td>
<td>Improves memory, vasodilator</td>
<td>Aspirin</td>
<td>II</td>
<td>Increased risk of bleeding</td>
<td>Rosenblatt et al., 1997; Gianni, 1998</td>
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<td></td>
<td></td>
<td>Clopidogrel</td>
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<td>Ticlopidine</td>
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<td></td>
<td></td>
<td>Digoxin</td>
<td>II</td>
<td>Increased bioavailability of digoxin</td>
<td>Mauro et al., 2003</td>
</tr>
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<td></td>
<td></td>
<td>Diliazem</td>
<td>III</td>
<td>Increased bioavailability of drug</td>
<td>Ohnishi et al., 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ibuprofen</td>
<td>I</td>
<td>Intracerebral mass bleeding due to inhibition of platelet aggregation</td>
<td>Mesel et al., 2003</td>
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<td></td>
<td></td>
<td>Nicardipine</td>
<td>II</td>
<td>Induction of CYP3A4 leading to decreased activity of drug</td>
<td>Shimozaka et al., 2002</td>
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<td></td>
<td></td>
<td>Phenytin</td>
<td></td>
<td>Fatal seizures</td>
<td>Kupiec and Raj, 2005</td>
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<td></td>
<td></td>
<td>Omeprazole</td>
<td>III</td>
<td>Induction of CYP2C9</td>
<td>Yin et al., 2004</td>
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<td></td>
<td></td>
<td>Thiazide diuretics</td>
<td>III</td>
<td>Increase in blood pressure</td>
<td>Shaw et al., 1997</td>
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<td></td>
<td>Trazodone</td>
<td>II</td>
<td>Induction of CYP3A4</td>
<td>Dergal JM, et al., 2002; Galluzzi et al., 2000</td>
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<tr>
<td></td>
<td></td>
<td>Warfarin</td>
<td>I</td>
<td>Increased risk of bleeding</td>
<td>Engelsen et al., 2003; Gianni and Dreitlein, 1998</td>
</tr>
<tr>
<td>Green tea (CAMELIA SINENSIS)</td>
<td>Cancer, heart problems, inhibits platelet aggregation</td>
<td>Warfarin</td>
<td>I</td>
<td>Increased risk of bleeding</td>
<td>Taylor et al., 1999</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Plant</th>
<th>Effect</th>
<th>Drug Interaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guarana (PAULLINIA CUPANA)</td>
<td>Cognitive improver, antioxidant, antibacterial</td>
<td>Caffeine/Respiratory stimulants</td>
<td>Potentiation of activity</td>
</tr>
<tr>
<td>Guggul</td>
<td>Lipid lowering activity</td>
<td>Diltiazem/Propranolol</td>
<td>Decreases the bioavailability of drugs</td>
</tr>
<tr>
<td>Kava (PIPER METHYSTICUM)</td>
<td>Anxiolytic, antidepressant</td>
<td>Alprazolam</td>
<td>Potentiation of sedation</td>
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<td></td>
<td></td>
<td>Anesthetics</td>
<td>Prolongation of anesthesia</td>
</tr>
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<td></td>
<td></td>
<td>Levodopa</td>
<td>Antagonism</td>
</tr>
<tr>
<td>Lemon balm (MELISSA OFFICINALIS)</td>
<td>Depression, nervous insomnia, antioxidant</td>
<td>CNS depressants</td>
<td>Additive CNS effects</td>
</tr>
<tr>
<td>Sage (KALVIA MIGHTORRIZA)</td>
<td>Insomnia, Blood purifier</td>
<td>Warfarin</td>
<td>Increased risk of bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diazepam</td>
<td>Induction of enzymes</td>
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<tr>
<td>St.John’s wort (HYPERICUM PERFORATUM)</td>
<td>Antidepressant and antiviral</td>
<td>Amitryptiline</td>
<td>Induction of CYP3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclosporine</td>
<td>Induction of CYP3A4 and P-gp; leading to decrease in drug concentration and rejection of transplanted organ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digoxin</td>
<td>Induction of P-gp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fexofenadine</td>
<td>Inhibition of P-gp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indinavir, Saquinavir</td>
<td>Induction of CYP 3A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irinotecan</td>
<td>Decreased concentration of drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loperamide</td>
<td>Acute delirium – mechanism unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methadone</td>
<td>Induction of CYP 3A4, 2C8 and CYP 2D6 leading to decrease in drug concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral Contraceptives</td>
<td>Failure of contraception due to induction of CYP3A4</td>
</tr>
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<td>Piroxicam</td>
<td>Photosensitizing drugs</td>
</tr>
<tr>
<td>Herb</td>
<td>Possibility</td>
<td>Effect</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Quazepam</td>
<td>III</td>
<td>Induction of CYP 3A4</td>
<td>Kawaguchi et al., 2004</td>
</tr>
<tr>
<td>Sertraline</td>
<td>I</td>
<td>Inhibits vesicular uptake of monoamines leading to serotonergic syndrome</td>
<td>Roz et al., 2002</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>I</td>
<td>Induction of CYP3A4</td>
<td>Sugimoto et al., 2001</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>II</td>
<td>Immune graft rejection due to induction of CYP enzymes</td>
<td>Mai et al., 2003</td>
</tr>
<tr>
<td>Theophylline</td>
<td>II</td>
<td>Induction of CYP1A2 leading to decreased concentration of drug</td>
<td>Nebel et al., 1999</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>III</td>
<td>Elevation of TSH levels</td>
<td>Ferko and Levine, 2001</td>
</tr>
<tr>
<td>Venlaxafine</td>
<td>I</td>
<td>Serotonin syndrome – Inhibition of serotonin reuptake and MAO Inhibition</td>
<td>Prost et al., 2000</td>
</tr>
<tr>
<td>Verapamil</td>
<td>III</td>
<td>Induction of CYP3A4, leading to decreased bioavailability</td>
<td>Tammergren et al., 2004</td>
</tr>
<tr>
<td>Warfarin</td>
<td>II</td>
<td>Induction of CYP3A4 and CYP2C9</td>
<td>Jiang et al., 2004</td>
</tr>
<tr>
<td>Valerian (VALERIANA OFFICINALIS)</td>
<td></td>
<td>Muscle relaxant, insomnia, GIT pains</td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>1</td>
<td>Additive sedation</td>
<td>Wiley, 1995</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1</td>
<td>Inhibition of delta – ALA – D activity</td>
<td>Dalla et al., 2008</td>
</tr>
<tr>
<td>Yohimbine (PAUSINYSTALIA YOHIMBE)</td>
<td></td>
<td>Antidepressant, erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>1</td>
<td>Increased blood pressure</td>
<td>Lacombiez et al., 1989</td>
</tr>
</tbody>
</table>

* I – herbs having higher possibility of co-administration with drugs; II – herbs having moderate possibility of co-administration with drugs; III – herbs having less possibility of co-administration with drugs
Interactions between Other Herbs and Drugs

Artemisinin
Artemisinin, an antimalarial herb is reported to induce its own elimination and that of omeprazole through an increase in CYP2C19 activity (Svensson et al., 1998).

Foeniculum vulgare
The antidiabetic herb Foeniculum vulgare has been reported to decrease the rate of absorption of ciprofloxacin due to chelation of the drug by the metal ions present in the plant extract (Zhu et al., 1999).

Liquorice
Liquorice is used as a natural sweetening agent and also for treatment of gastric ulcers. It can interact with antihypertensive drugs leading to synergistic effect (Cumming et al., 2003); hydrocortisone leading to pseudoadosteronism (Beate et al., 1999); oral contraceptives leading to hypertension, edema and hyperkalemia (Gerry et al., 1997).

Silymarin
Silymarin is being used for more than 2000 years to treat liver, gall bladder disorders, including hepatitis, cirrhosis, and jaundice and to protect liver against poisons from chemical and environmental toxins (Vladimir and Daniela, 2005). Silymarin is reported to potentiate the effects of antihypertymic drugs (Gyynos et al., 2001), increase the pharmacological activity of cisplatin (Scambia et al., 1996), decrease the blood concentrations of indinavir (Piscitelli et al., 2002), losartan (Han et al., 2009) and metronidazole (Chon et al., 2005).

Herbs used by women

Women periodically experience changes with menstrual regularity, an absence of a menstrual cycle (amenorrhea), premenstrual tension, bloating, cramping and mood fluctuations (dysmenorrhea), flooding and heavy cycles (menorrhagia), fluid retention, irritability, migraines, skin problems, irregular or heavy menses, pelvic congestion, fibroids, endometriosis and cysts. Herbal medicines provide gentle support to women by nourishing reproductive tissues and regulating hormones secreted by the pituitary and adrenal glands. These hormones influence ovarian function, regulate menstrual flow, minimize cramping and stabilize mood changes. Herbs are also used by women to support liver function, which facilitate in breaking down excess circulating hormones, to accelerate their removal from the body, to minimize fluid retention and to provide direct antispasmodic action for pain management and cramping. The herbs like False Unicorn (Chamaelirium luteum), Partridge Berry (Mitchella repens), Chaste berry (Vitis agnus castus), Motherwort (Leonurus cardiaca), Red Raspberry (Rubus idaeus) are used as reproductive tonics. Herbs like Dong Quai (Angelica sinensis), Black cohosh (Cimicifuga racemosa), Mugwort (Artemisia vulgaris), Rue (Ruta graveolens) are used as emmenagogues, which stimulate, regulate and promote a normal menstrual flow. The herbs like Shepherds Purse (Capsella bursa pastoris), Cayenne (Capsicum minimum), Lady’s Mantle (Alchemilla vulgaris), Beth Root (Trillium erectum) are used to reduce or eliminate fluid retention associated with premenstrual tension by increasing the flow of urine. Chamomile, Dandelion and Dong quai are the herbs widely used by women which have interaction potential with the drugs. Studies reveal chamomile administration with opioids leads to increased CNS depression (Ahebe et al., 2002), dandelion if co –administered with diuretic drugs can potentiate the diuretic effect (Akhshar, 1985), Dong quai (Angelica dahurica) is reported to increase the Cmax and AUC of diazepam along with an increase in half of tolbutamide (Ishihara et al., 2000).

Weight loss supplements
The weight loss supplements like ephedra and germander have interaction potential with drugs. Ephedra can increase the risk of gastric lesions when co-administered with loxoprofen (Chou et al., 2002). It is evident from clinical reports that ephedra can increase the risk of seizures when co – administered with anticonvulsants (Spinella, 2001). Germander, another weight loss supplement can lead to liver damage when co – administered with dexfenfluramine (Mostefa et al., 2000).

Herbs Proven to Alter Cytochrome P450 Enzymes in In - Vitro Models

Cytochrome P450 (CYP) enzymes are involved in the metabolism of a multitude of drugs. These enzymes are involved in numerous interactions between drugs and food, herbs and other drugs. The observed induction and inhibition of CYP enzymes by natural products in the presence of a prescribed drug can result in adverse effects. In vitro studies reveal that herbal medicines and their biomarkers have potential to modulate the - CYP enzymes. These evidences need support in the form of systematic studies, so that metabolism – based interactions can be predicted and avoided more readily in clinical applications or by health care professionals (Delgoda and Westlake 2004). The potential of herbs to induce/inhibit the CYP enzymes in various in vitro models are summarized in Table 3.
Table 3. Herbs proven to alter cytochrome P450 enzymes in in - vitro models.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Herb Indication</th>
<th>CYP Enzyme</th>
<th>In - vitro model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANGELICA DAHURICA</td>
<td>Analgesic, Diuretic, Antibacterial</td>
<td>Inhibits CYP3A4</td>
<td>Inhibits multidrug-resistant and methicillin-resistant strains of Staphylococcus aureus Liver microsomes</td>
<td>Lechner et al., 2004, Guo et al., 2001</td>
</tr>
<tr>
<td>Devil’s Claw (RHAPGOGOPHYTUM PROCUMBENS)</td>
<td>Arthritis, sedative</td>
<td>CYP2C8, CYP2C19, CYP3A4, CYP1A2, CYP2D6</td>
<td>Human kidney (HK-2) proximal tubule cell line</td>
<td>Nadia et al., 2009</td>
</tr>
<tr>
<td>Echinacea (ECHINACEA PURPUREA)</td>
<td>Immunomodulator</td>
<td>Inhibits CYP2C19, CYP2D6</td>
<td>Baculovirus expressed CYP enzymes</td>
<td>Modarai et al., 2007</td>
</tr>
<tr>
<td>Garlic (ALLIUM SATIVUM)</td>
<td>Reduces cholesterol levels</td>
<td>Inhibits CYP2C9, CYP2C19, CYP3A4 Inhibits CYP2E1</td>
<td>Human liver microsomes CYP 3A4 Substrates (7-Benzoxynorversion and 7-ethoxy-3 cyanocoumarin Rat liver microsomal cytochrome P450 fractions</td>
<td>Greerball et al., 2006, Foster et al., 2001, Caro and Cederbaum, 2005</td>
</tr>
<tr>
<td>Ginseng (PANAX GINSENG)</td>
<td>Immunomodulator</td>
<td>Inhibits CYP1A2, CYP2B1, CYP2C9, CYP3A4</td>
<td>DNA-expressed cytochrome P450 enzyme catalytic activity</td>
<td>Henderson et al., 1999</td>
</tr>
<tr>
<td>Goldenseal (HYDRASTIS CANADENSIS)</td>
<td></td>
<td>CYP2D6, CYP3A4, CYP3A5</td>
<td>Caco – 2 cell lines</td>
<td>Chatterjee and Franklin, 2003</td>
</tr>
<tr>
<td>Kava (Piper methysticum)</td>
<td>Anxiety, depression</td>
<td>Inhibits CYP3A4, CYP1A2, CYP2C9, CYP2D6</td>
<td>Human liver microsomes</td>
<td>Mathews et al., 2002, Mathews et al., 2005</td>
</tr>
<tr>
<td>Liquorice (GLYCYRRHIZA GLabra)</td>
<td>Expectorant, antioxidant, allergic inflammation</td>
<td>CYP3A4, CYP2C9</td>
<td>Human recombinant enzymes</td>
<td>Kent et al., 2002, Sachiko et al., 2005</td>
</tr>
<tr>
<td>Saw palmetto (SERENOA REPENDS)</td>
<td>Benign Prostatic Hyperplasia</td>
<td>Inhibits CYP3A4, CYP2C9 and CYP2D6</td>
<td>Healthy volunteers</td>
<td>Yale and Glurich, 2005</td>
</tr>
<tr>
<td>Schizandra (SCHIZANDRA CHINENSIS)</td>
<td>Sedative, Diuretic</td>
<td>Inhibits CYP3A4</td>
<td>Liver microsomes</td>
<td>Iwata et al., 2004</td>
</tr>
<tr>
<td>Silymarin (SILYBUM MARIANUM)</td>
<td>Hepatoprotective</td>
<td>Inhibits CYP3A4, CYP2C9</td>
<td>Human hepatocytes/ Human recombinant enzymes</td>
<td>Venkataramanan et al., 2000</td>
</tr>
<tr>
<td>Valerian (VALERIANA OFFICINALIS)</td>
<td>Insomnia, Muscle relaxant</td>
<td>Inhibits CYP3A4, CYP2C9 and CYP2C19</td>
<td>Human recombinant enzymes</td>
<td>Tania et al., 2004</td>
</tr>
<tr>
<td>Vinca (CATHARANTHUS ROSEUS)</td>
<td>Anticancer</td>
<td>Inhibits CYP2D6</td>
<td>Human Liver Microsomes</td>
<td>Usia et al., 2005</td>
</tr>
</tbody>
</table>

* I – herbs having higher possibility of co – administration with drugs; II – herbs having moderate possibility of co – administration with drugs; III – herbs having less possibility of co – administration with drugs
Predicted Herb - Drug Interactions

Perusal of available literature reveals many theoretical herb - drug interactions, which are based on assumptions and which lack sound scientific evidences. These interactions are based on activity of constituents contained in herbs or herbs having similar pharmacological potential as that of the drugs or herbs having toxic potential similar to drugs. These theoretical considerations may/may not confer that they will produce an interaction in vivo.

Laxative herbs like senna, aloe, cascara etc increase motility of gastrointestinal tract and hence they may increase the elimination rate of drugs. Senna, widely used herbal laxative is known to decrease the serum concentration of digitalis (Botzler, 1982). Herbs can also alter the absorption of drugs. It is believed that absorption of iron formulations can be inhibited by saw palmetto (Serenoa repens) and the saponins present in the sarsaparilla (Smilax ornata) plant can increase the absorption digitalis and bismuth which can lead to toxic symptoms.

The herbs and drugs having similar pharmacological profile when co – administered can lead to potentiation of pharmacological effect. If sedative herbal medicines like hops (Humulus lupulus), kava (Piper methysticum), valerian (Valeriana officinalis), bupleurum (Bupleurum falcatum) are co – administered with the sedative/anxiolytic drugs then there is a possibility for potentiation of sedative effect. A case report leading to semi - comatose condition in a 54 yr old patient has been documented who was concomitantly using kava and alprazolam (Almeida and Grimsley 1996). This case report suggests that it is sensible to avoid the use of sedative herbs like hops, chamomile, kava and valerian along with the sedative drugs. Similarly the herbs having central nervous stimulatory effect can lead to enhanced stimulation of nervous system if co – administered with the central nervous system stimulant(CNS) drugs. Theoretically, co – administration of kola – nut along with theophylline can lead to potentiation of CNS effects. In similar lines herbs used as diuretics should not be concomitantly used with diuretic drugs. As a general concept it is preferable to avoid the combinative usage of the herbs and drugs having similar toxic potential. Most of the available literature cautions that there is greater chance for potentiation of hepatotoxicity when hepatotoxic herbs like chaparral (Larrea tridentata), germander (Teucrium chamaedrys), echinacea (Echinacea purpurea) are co – administered with hepatotoxic drugs such as non steroidal anti–inflammatory drugs (NSAIDs), ketoconazole and methotrexate.

Herb - drug combinations can also lead to antagonism of drug activity if they have opposing mechanism of actions. It is speculated that the activity of dopamine containing drugs may be antagonized by the kava due to its dopamine antagonistic properties.

Herbs altering the electrolyte balance in the body can alter the pharmacokinetics/pharmacodynamics of drugs which mediate their actions through the ionic mechanisms. The herbs such as liquorice and herbal laxatives alter the ionic concentrations in the body can lead to alteration in the activity of drugs like digitalis, antihypertensive and diuretic drugs.

Herbs have potential to alter the intraoperative complications and also postoperative complications (Ang-Lee et al., 2001; Denon and Deborah 2003). These herbs may alter the effects of anesthesia or may alter the kinetics/dynamics of postoperative medications. This interaction of potential of herbs with anesthetics and postoperative medications stresses the need to avoid usage of herbal medicines, well in advance before any surgical intervention. In certain cases herbs have potential to enhance the intraoperative bleeding. A case report of severe intraoperative bleeding has been reported in a patient consuming Saw palmetto (Cheema et al., 2001). Another case report of cardiovascular collapse has been reported in a patient during induction of anesthesia and the possible mechanism has been attributed to long term consumption of St.John’s wort (Samuel and Junj, 2000).

Long-term use of ephedra is known to deplete the endogenous catecholamines which can cause intraoperative hemodynamic instability and life-threatening interaction with monoamine oxidase inhibitors (Ling et al., 1995). Hence anesthetists specify discontinuation of ephedra usage at least 24 hours prior to any surgical intervention. Feverfew, garlic, ginger and ginkgo have potential to increase the risk of bleeding due to their platelet inhibition potential (German et al., 1995; Norred and Finlayson, 2000). A case report of post operative bleeding had been reported with the use of ginkgo biloba in a liver transplant patient (Hausser et al., 2002). Hence it is safe to discontinue the usage of these herbs 1 week before surgery and use of ginkgo at least 36 hours before surgery. Ginseng can produce hypoglycemia,
can increase the risk of bleeding and it also has potential to decrease anticoagulation effect of warfarin therefore usage should be avoided at least 1 week prior to surgical intervention (Norred and Finlayson, 2000). St. John’s wort may prolong effects of anesthesia and it has potential to induce cytochrome P450 enzymes, which may affect the kinetics of several classes of drugs. It is prudent to avoid usage of St. John’s wort at least 5 days before any surgical intervention. Kava and valerian may increase sedative effect of anesthetics and kava usage should be avoided at least 1 day before surgical procedure (Saha et al., 2001). It is reported that Dong quai (Angelica sinesis) is the cause of hypertension in a 32-year-old woman with 3 weeks post-partum (Nambiar et al., 1999). The platelet inhibitory potential of Aloe vera is reported to be the cause of massive intraoperative bleeding in a 35 yr old woman who was consuming Aloe vera tablets (Lee et al., 2004). Goldenseal (Hydrastis canadensis) can worsen edema or hypertension, liquorice may cause high blood pressure, swelling or electrolyte imbalance, hence it’s wise to avoid the use of this herb prior to surgery because the post and preoperative data are not available for this herb (Deron and Debonah, 2003).

**The other Side of Herb – Drug Interactions**

Along with an exhaustive list of herb – drug interactions which need special precautions there are some herb - drug combinations which are quite safe. In some cases, herbs have been shown to mitigate or prevent adverse effects associated with drugs. For example, aromatic herbs such as ginger can be used to prevent drug-induced nausea; milk thistle can be used to prevent the liver toxicity associated with drugs. In addition, the scientific studies have proven that capsaicin reduces gastric mucosal damage induced by aspirin (Yeoh et al., 1995) and St. John’s wort doesn’t interact with carbamazepine, pravastatin, mycophenolate mofetil (Sugimoto et al., 2001; Bolley et al., 2002; Mai et al., 2003). Hawthorn is useful for angina and it is as an alternative to digitalis in Europe. A study on digoxin and hawthorn revealed that their combined use has no significant interaction and they can be used safely (Tankanow et al., 2003). Animal studies have shown that the combination of aqueous extract of Chinese medicinal plant Tripterygium wilfordi and cyclophosphamide significantly increases the heart and kidney allograft survival compared to cyclophosphamide alone (Wang et al., 2000). It is also proven that garlic prevents the formation of toxic metabolites of paracetamol, co – administration of ginkgo with antipsychotics (haloperidol) in chronic schizophrenic patients reduces extra pyramidal side effects associated with haloperidol (Sasaki et al., 2000; Zhang et al., 2001). *Centella asiatica* can also be used as an adjunctive medication for patients with epilepsy due to its additive anticonvulsant activity (Vattanajun et al., 2005). *Momordica charantia* is reported to augment the hypoglycemic effect of rosiglitazone which can be used to reduce the dose of rosiglitazone to achieve enhanced therapeutic effect with minimum side effects (Saha et al., 2009). Piperine can be used as bioavailability enhancer for several drugs and studies bolster that piperine enhances the bioavailability of pravastatin which can be used as a means to achieve better therapeutic control and improved patience compliance (Bano et al., 1999). In the similar lines Ginseng is considered to be potent adjuvant for delivery of vaccines which have been proven to induce higher or similar antibody titres than vaccines adjuvanted with aluminium hydroxide (Rivera et al., 2003). Further, studies also prove that Rosemary (Rosmarinus officinalis) has chemopreventive effect as it increases efflux and intracellular accumulation of doxorubicin and vinblastine (Huang et al., 1994). In vitro studies also revealed that silybinin enhances the antitumour activity of cisplatin (Scambia et al., 1996). All these data suggest that synergistic potential between herbal medicines and drugs can be therapeutically advantageous, clearly stressing the need for extensive work to be done in this area.

**Conclusion**

People use herbal medicines so as to ensure general health and nutrition. The magnitude of herb – drug interactions are less common when compared to drug – drug interactions. Recent estimates also specify that drug – drug interactions are considered to be the fourth leading cause of death in hospitalized patients. In spite of the vast majority of drug – drug interactions which are documented most commonly, the downplaying attitude of allopathic physicians elevates the concern on herb – drug interactions which occur very rarely. Till date the interactions of St.John’s wort, ginkgo, ginseng, garlic and ephedra with drugs are of major concern because of the magnitude of evidence available. A close look into the herb – drug interactions reveal that most of them are based on excess consumption of herbs, irrational use in geriatric patients, a few case reports on patients/healthy volunteers and few scientific studies conducted in animals. Many of the herb – drug interactions die unnoticed by the physicians until an adverse effect or adverse event occurs. In comparison with the drug – drug interactions the extent of herb – drug interactions is not alarming but there is a great concern about safety of herbal medicine. In spite of the entire herb – drug interactions listed there are certain herb – drug combinations which are safe, certain combinations which increase the bioavailability of drugs, prevent formation of
toxic metabolites of drugs, which can be used as adjuvants to deliver vaccines. In view of this, there is an urgent need to critically evaluate herb – drug interactions along with an equal responsibility on healthcare professionals to highlight the safe herb – drug combinations and to establish the safety of herbal medicine. The new evidences in support of herb – drug interactions will dispel the fears about usage of certain herb - drug combinations, can guide in support of herb – drug interactions will dispel the fears about usage of certain herb - drug combinations, can guide to monitor the therapeutic regimens of drugs and to avoid concomitant use of herbs and drugs which are harmful.

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