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Herbal Drug Interactions

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***Abstract*: Herbs have been used since ages for the treatment of various diseases. As herbs are obtained from plants and are a naturally occurring source, people considered it safe. They are not aware about the interaction of herbal medications that will lead to several side effects. The administration of herbal medicines in combination with therapeutic drugs causes the interaction between phytochemicals present in herbal medicines and active ingredients in prescribed drugs that leads to herb-drug interactions. The interactions may be pharmacodynamics and pharmacokinetics. Nowadays people self-administer herbal medicines. It is observed that many individuals who use herbal medicines do not report that to their physician and pharmacist. This review focuses on the interaction of herbal medicine and risk associated when herbs such as Ginkgo (Ginkgo biloba), Garlic (Allium sativum), Kava (Piper methysticum), Echinacea (Echinacea purpurea), Danshen (Salvia miltiorrhiza), St.John's wort (Hypericum perforatum) use in combination with therapeutic agents. To make people, physicians and pharmacists aware about herb-drug interactions, pharmacological actions and side effects associated with it.**

***Keywords*: Herb-drug interaction, Herbal medicines, Pharmacokinetic, Pharmacodynamic.**

1. Introduction

Herbal drugs play many roles in our daily life, like dietary products and in preparing food at home, etc. Herb-drug interaction leads to pharmacological modification. The drug use along with herbs may show pharmacodynamic and pharmacokinetic interactions. Pharmacokinetic interaction causesalteration in absorption, distribution, metabolism and elimination. Similarly, pharmacodynamic interaction causes additive or synergistic or antagonist effect on the drugs or vice versa. Researchers had demonstrated that herbs show the toxicities and drug interactions like other pharmacologically active compounds. Herbal products are considered best choice as complementary medicine in western countries, especially in United state and Europe. All herbal medicines and dietary supplements are a complex mixture containing multiple active phytocomponents that increase the possibility of herbal drug interaction. Herbal drugs can cause different disease but it is also used in treatment of various disease.

Herb-drug interactions are based on the same pharmacological principles as drug-drug interactions. In contrast to single compound-containing allopathic medicinal products, herbal medicines usually contain a complex mixture of phytochemicals that are produced as secondary metabolites. Pharmacokinetic interactions specifically refer to changes (i.e. enhancement or inhibition) in the absorption, distribution, metabolism, and excretion of drugs instigated by the co-administered herbal medicine, while pharmacodynamic interactions include synergistic or antagonistic pharmacological effects.

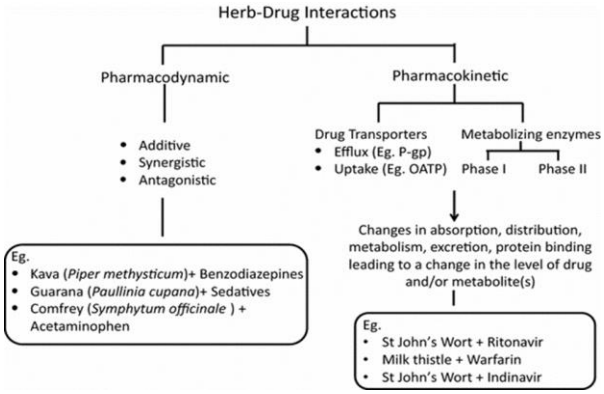

Fig. 1. Mechanisms of herb-drug interaction

2. Mechanisms Involved in Herb-Drug Interaction

A. Pharmacokinetic Interaction

1) P-Glycoprotein (P-gp)

The absorption, distribution and elimination/reabsorption of many clinically important therapeutic substances are regulated by P-gp family proteins. Direct interaction with binding sites on the P-gp molecule takes place through competitive or non-competitive inhibition or induction of the outflow of drugs, due to modulation of P-gp by herbal constituents. The pharmacokinetic interaction based on P-gp occurs mainly by depletion\reduction of energy required for driving the translocation of P-gp-bound drug substrate, which takes place due to inhibition of ATP binding, hydrolysis or coupling of ATP-hydrolysed molecules by the phytochemicals present in herbs.

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2) Herb-drug interactions at metabolism level

At metabolism level, enzymes responsible for the metabolism of synthetic drugs or their transporters are either inhibited or induced by herbal products, which cause HDIs. The enzyme degrades, deactivates or conjugates to drugs before excretion. The inhibition or induction of this enzyme by herbs causes HDIs.

3) Enzyme inhibition

Inhibition can be of two types, like, reversible inhibition and irreversible inhibition. The systemic exposure of the victim drug due to a decrease in metabolic clearance and/or increase in bioavailability is distinct by reversible inhibition. Competitive inhibition occurs when herb binds to the active sites of the enzyme and prevents the binding of synthetic drug and enzyme. Irreversible inhibition is characterised by time-dependent inhibition or mechanism-based inhibition. Irreversible noncovalent binding of an herb to the enzyme takes place in irreversible inhibition.

4) Enzyme induction

Cause of enzyme induction, plasma concentration of drug reaches subtherapeutic levels. Toxicity may be due to intensified blood levels caused by induction of drug transporter. The enzyme induction by herbs may result in a reduction of serum drug concentrations and if metabolite is active, it may result in toxicity.

5) Pharmacodynamic interactions

Pharmacodynamic interactions are either synergetic or antagonistic. Synergistic interaction potentiates the action of synthetic drug. Antagonistic interaction reduces the efficacy of synthetic drugs. Pharmacodynamic interactions between herbs result from drug mixtures, as one of the drugs changes the effect of another drug. Pharmacodynamic interactions may be due to additive or synergistic effects that may lead to overgrowth of effect or toxicity, or herbal medicinal products having properties contrary to the effect of drugs that are antagonistic and lead to therapeutic failure. Additive or synergistic effects result when administration of more than one drug having similar pharmacological effect has competition to produce greater effect. Antagonistic effect results when combination of two or more drugs may lead to decrease the effect of one drug or both the drugs. The interaction of herbal products with hepatic enzymes can also result in pharmacodynamic effects. The warfarin interactions are the classical example of pharmacodynamic interactions. It is observed that warfarin shows increased anticoagulant effect when administered with anticoagulant herb or antiplatelet herb such as Ginger, Garlic, Ginkgo biloba. Vitamin K containing herbs antagonize the effect of warfarin by reducing the blood clot. Ginger interactions with conventional drugs are pharmacodynamic interactions. Interaction of Garlic with antihypertensive and antidiabetic drugs is mostly pharmacodynamics and when it combines with glibenclamide i.e., antidiabetic drug it causes increased hypoglycemic effect. Ginkgo biloba inhibits platelet aggregation and when combined with warfarin causes bleeding. Kava has pharmacodynamic interaction with CNS depressant and anticonvulsant drugs. When Kava is given in combination with alprazolam it may have additive effects on GABA receptors and causes drowsiness. The pharmacodynamic interaction may occur when John's wort (SJW) is given in combination with serotonergic agent and other antidepressants.

3. Some Examples of Herbal Drugs

1) Echinacea

- Common name: eastern purple flower
- Scientific name: Echinacea purpurea
- Family: Daisy family or Asteracea
- Chemical constituent: Glycosides, Echinacin, Polysaccharide, Caffeic acid, volatile oils, Flavonoids, Essential oils, etc.
- Uses: Anti-microbial, Immunomodulatory, Hepatoprotective, Skin care, Anti-diabetic, Anti-oxidative, etc.

2) Ginseng

- Common name: man-root
- Scientific name: Panax ginseng
- Family: Araliceae
- Chemical constituent: Ginsenosides, Panaxosides, Dammarol, Resins, Essential oils, Volatile oils, starch, etc.
- Uses: Demulcent, Improve stamina, Expectorant, Emetic, Stimulant, Carminative, also in treatment of Insomnia, Loss of appetite, Diabetes.

3) Ginkgo biloba

- Common name: maidenhair tree
- Scientific name: Ginkgo biloba
- Family: Ginkgoaceae
- Chemical constituent: Flavanols, Flavone glycosides, Lactone derivatives, Bilobalide, Ascorbic acid, vanillic acid, Catechin, etc.
- Uses: It is used in treatment of Altitude sickness, Cerebral vascular, Cognitive disorder, Dementia, Glaucoma, Memory loss, Premenstrual syndrome, etc.

4) Turmeric

- Common name: Haldi
- Scientific name: Curcuma longa
- Family: Ginger family Zingiberaceae
- Chemical constituent: 5% curcumanoids as coloring matter which contain curcumin I, curcumin II and curcumin III, 5% volatile oils which contain alcohol and ketone and monoterpene.
- Uses: anti-inflammatory for treatment of skin conditions, also used to treat pain in the body, ringworm, bruising, leech bites, eye infections, infected wounds, joint pain, arthritis, improves digestion, boosts immune system, etc.

5) St. John's wort

- Common name: hypericum, Klamath weed
- Scientific name: Hypericum perforatum
- Family: St. john's wort
- Chemical constituent: Phenylpropanes, flavonol derivatives, Xanthones, some amino acids, naphthodianthrones, essential oils, etc.

- Uses: Effective dietary supplement in nervous system disorder, Anti-diarroheal, Rheumatism, Anti-depressant, Treatment of wounds, Back pain, Groin pain, etc.

6) Elderberry

- Common name: Black elder, Boor tree, BlackBerry elder
- Scientific name: Sambucus
- Family: Moschatel
- Chemical constituent: Polyphenols like Chlorogenic acid, Neochlorogenic acid, Quercetin, Sambubiose, etc.
- Uses: Anti-inflammatory, Potent anti-cancer, treat respiratory illness, Natural support for arthritis, used in chronic fatigue syndrome, for HIV\AIDS and boosting the immune system, etc.

7) Valerian

- Common name: Garden heliotrope
- Scientific name: Valeriana officinalis
- Family: Valerianaceae
- Chemical constituent: Sesquiterpenes of volatile oil (include valeric acid), Iridoids (valepotriates), alkaloids and free amino acids.
- Uses: treatment of insomnia\sleep disorder, Attention deficit hyperactivity disorder, Anxiety, Depression, Epilepsy, etc.

4. Clinical Test\Cases about Disorder\Treatment Related to Herb-Drug Interaction

Here are some herbal drugs interaction cases

1) Danshen (Salvia miltiorrhiza)

It is used as an antibacterial, antioxidative, antineoplastic, anti-inflammatory. It contains diterpenoids, phenolic acid, caffeic acid, salvianolic acid, essential oils, etc.

- Case1: case reported that interaction between warfarin and danshen, leading to increase an INR (international normalized ratio), which potentiated anticoagulant effect of warfarin and increased risk of bleeding
- Case2: Interaction of danshen and warfarin concomitant (naturally) leads to abnormalities of clotting in patient having rheumatic heart disease.

2) Echinacea (Echinacea purpurea)

It contains alkamides, cichoric acid, phenolic acid, etc. It shows different properties like anti-inflammatory, larvicidal activity, antibacterial and antiviral activity, etc.

Case: In in vivo clinical studies, 12 healthy subjects were dosed 1600 mg/day with E. purpurea extracts (for 8 days) along with caffeine, tolbutamide and midazolam to evaluate CYP1A2, CYP2C9 and CYP3A enzyme activities, respectively. The results obtained showed Echinacea extract inhibited hepatic CYP1A2 and CYP2C9, and induced CYP3A4 enzyme activity, which lead to 27% decrease in caffeine CL/F, 12% decrease in tolbutamide CL/F and 42% increase in the systematic clearance and reduced AUC by 23% of midazolam respectively.

3) Garlic (Allium sativum)

It mainly contains organosulfur compounds like allicin, diallyl disulfide, diallyl trisulfide, S-allyl cysteine. It is used as antihyperlipidemic, antiprotozoal, immunomodulatory activity, etc.

- *Case1*: The two in vivo pharmacokinetic trials were conducted to study the effect of garlic on the antiviral drug saquinavir. The study found that ingestion of garlic increased expression of duodenal P-gp to 131% in subjects. The average AUC and Cmax of saquinavir was decreased by garlic up to 51% and 54%.
- *Case 2:* Clinical study shows that the intake of S-allyl cysteine (active constituent of garlic) inhibits platelet aggregation. Inhibition of platelet aggregation shows an additive anticoagulant effect, which is a possible mechanism for warfarin and garlic interaction, which ultimately increases the anticoagulant effect. Increased anticoagulant may increase the risk of bleeding.

4) Ginkgo (Ginkgo biloba)

Ginkgo Biloba leaf contains flavonol glycosides and terpene trilactones, proanthocyanin and organic acids. G. biloba leaf extract is used in the treatment of Alzheimer's disease, neurodegenerative disease, cerebral insufficiency, neurosensory problems, eye ailments, vascular insufficiencies, age-related memory deficit and oxidative stress, anti-angiogenesis, anti-inflammatory, and anti-asthmatic.

- *Case1:* In in vivo clinical trials, 10 healthy volunteers were given G. biloba extract (GBE) to test its effect on CYP2C9 using tolbutamide as a probe. The AUC for tolbutamide after taking GBE was reduced by 16% as compared to AUC before use of garlic along with tolbutamide. It is a minor interaction.
- *Case 2:* An open-label study in healthy volunteers showed a decrease in the AUC and Cmax of midazolam by 34% and 31% respectively when used along with GBE. This research found that GBE induces CYP3A metabolism, which leads to a decrease in midazolam concentrations.
- *Case 3:* In a case study, fatal seizures were reported with anticonvulsant medications like valproic acid. GBE has been reported to induce CYP2C19 enzyme activity. The CYP450 enzyme is reported to metabolize valproate, chiefly by CYP2C9 and CYP2C19. Thus, this coadministration of valproic acid and Ginkgo biloba extract should be prevented.

5) Kava (Piper methysticum)

Kava contains kavain, dihydrokavain, methysticin, dihydromethysticin, demethoxyyangonin, and yangonin. Kava has a beneficial effect in analgesia, neuroprotection, and anticonvulsant properties. Kava is also used in the treatment of anxiety.

- *Case1*: A case report in a 76-year-old Parkinson's disease patient showed reduced activity of levodopa (a precursor of dopamine). On further investigation, it was reported that the patient simultaneously consumed kava and dopamine, which lead to decrease in

dopamine efficacy (decreased dopamine level) due to an antagonizing property of kava.

6) St. John's wort (Hypericum perforatum)

The major active constituents present in St. John's wort are hyperforin and hypericin and also flavonoids, tannins and volatile oils. St. John's wort is used as an antidepressant, antiviral and antibacterial. It also shows sedative and astringent properties. It is used traditionally for the treatment of excitability, neuralgia, sciatica, fibrositis, anxiety, menopausal neurosis and depression and as a nerve tonic and topical application for wound treatment.

- *Case 1*: The case reported of serious organ rejection after transplantation due to simultaneous use of cyclosporine with SJW. The efficacy of cyclosporine is decreased, which causes rejection of organs. Thus, serious and potentially fatal interactions between cyclosporine and SJW are likely to occur via induction of CYP3A4 and/or P-gp by St. John's wort.

5. Conclusion

The use of herbal medications along with conventional drugs have proven to be dangerous. There is herb-drug interaction among the most commonly used herbs. Herbal medicines and dietary supplements are used in the world on a larger basis, this leads to an increase in the possibility of herb-drug interactions. The interactions of herbal medicines are life threatening. The cases reported show that most of the interactions of herbal medicines are associated with anticoagulant agents. Several other immune suppressants and benzodiazepines show herb-drug interactions. The new research has shown more light on the dangerous effect of herbal medicines for people on certain medications. Even after many studies, there is a need for more data to study about the pharmacokinetics and pharmacodynamics interactions of other herbs along with therapeutic drugs, so as to ensure patient safety. The health care professionals have to take into consideration the patient's medication history and should know if they are taking any herbal medicines. The physician or pharmacist needs to cooperate with patients so that they can tell about medications they are consuming besides the prescribed drugs. The main purpose of this review is that people should know about the side effects of herbal medicines and should not ignore all these problems and take it into consideration so it does not cause any trouble in future.

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