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HERBAL DRUG INTERACTIONS AND THEIR IMPACT ON PHARMACOKINETICS

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ABSTRACT

Herb–drug interactions are important issue for clinical therapeutic efficacy of medicine treatment. Herb–drug interactions affect either the pharmacokinetic fates or pharmacodynamics activities of drugs, leading to therapeutic failure or toxicities Unlike conventional drugs, herbal products are not regulated for purity and potency. Thus, some of the adverse effects and drug interactions reported for herbal products could be caused by impurities (e.g., allergens, pollen and spores) or batch-to-batch variability Pharmacokinetic interaction occurs when herbal drugs inhibit or decrease the normal activity level of drug transporters through a competitive or non-competitive mechanism. Interactions can also occur through the induction of transport proteins via the increase of the mRNA of the relevant protein. In this we have highlighted about the causes of herbal drug interactions and their article mechanisms with examples.

KEYWORDS: Herbsinteraction, amla, cinnamon, liquorice, ginseng, turmeric, ephedra, garlic, st.johnworts, patient counselling.

INTRODUCTION

Herbal products are medicines derived from plants. They are used as supplements to improve health and well being, and may be used for other therapeutic purposes. Herbal products are available as tablets, capsules, powders, extracts. Many people believe that products labeled "natural" are always safe and good for them. This is not necessarily true. The concurrent use of herbal medicines and allopathic drugs is one of the consequences. In western countries Herbal products are considered as the best choice as complementary medicine especially in the United States and Europe. There has been an increase in demand for “complementary” medicines, including those of plant origin. In public it has significant increase in the self-administration of herbal medicines. In the context of the growing demand and use of herbal medicines for patients these is due to herbal medicines and dietary supplements are a complex mixture that containing multiple active phyto-components. It can increase the possibility of herb-drug interaction [HDI].

Drug Interaction

Now a days the worldwide the variety of products are producing while increasing the risk of interaction. It causes an interaction between two drugs occur. If the effect of a drug is changed either qualitatively or quantitatively by another substance like herbal medicine/product/ingredient. New drugs may cause unpredictible interactions. Drug-related and disease-related factors (patient's age, gender, genetic characteristics, pathological condition), such as the posology and method of administration, pharmacokinetic, pharmacodynamic, and therapeutic properties of the drug. It is more common in the geriatric group aged 65 and over, and the use in women in this adult population is higher than in men.

- Inhibition of absorption
- Enzyme inhibition increase in risk of toxicity
- Enzyme inhibitors resulting in reduced drug effect
- Enzyme induction resulting in toxic metabolites
- Altered renal elimination

Many mechanisms play a role in these interactions, and interactions are seen in two main types

1. Pharmacokinetic parameters
2. Pharmacodynamic parameters

Pharmacokinetic Interactions

Pharmacokinetic interactions result in changes in drug absorption, distribution, metabolism, and elimination. These interactions lead to a decrease or increase in effect as a result of the change in drug concentration in body fluids. In case of pharmacokinetic interaction the plasma level or half-life of the drug should be determined experimentally. If the herbal products or its metabolites inhibit an enzyme involved in drug metabolism, it leads to either it increase the potential for toxic effects, or it will reduce the metabolism of drugs that metabolize the enzyme and turn it into an inactive metabolite as a result of metabolism.

If the herbal drug induces an enzyme, it reduce the drug effect, since the metabolism of the drugs that are metabolized by this enzyme and converted into inactive metabolite then metabolism will induce. Like that, if the drug turns into an active metabolite as a result of metabolism, if the herbal drug induces the enzyme it is responsible for the metabolism of the drug, it increases the drug effect or toxic effect and increased effective metabolite concentration. Pharmacokinetic interactions are the most common interactions as a cause of undesirable side effects.

Mechanisms that are involved in pharmacokinetic interaction

Pharmacodynamic Interactions

Pharmacodynamic interactions occur when one drug changes the effect of another drug that means effect opposite or in the same direction, chemically combined with it. If the herbal medicine and drug affect the same receptor or the same site, interaction occurs it is called synergic or antagonistic effect. The effect of the drug decreases or disappears as a result of the antagonistic effect, While the effect of the drug increases as a result of the additive effect. Pharmacodynamic interactions occur when a herbal product produces additive, synergistic, or antagonist activity in relation to drug without any change in the plasma concentration of either herbal product or conventional drug.

Mechanisms that are involved in pharmacodynamic interaction

- Additive pharmacodynamic effects
- Antagonistic pharmacodynamic effects

Pharmacokinetic Interactions

1. Inhibition of absorption

Some Drugs that act as binding agents it can impair the bioavailability of other drugs that can reduce the therapeutic effect of the drug it may be increased or decreased by drugs that increase stomach pH.

2. Enzyme inhibition increasing risk of toxicity

This is one of the most common mechanisms by which clinically important drug interactions occur in liver and intestine Most of the drugs are metabolized to inactive metabolites by enzymes. The Inhibition of this metabolism can increase the effect of the object drug. If the increase in effect is large enough, drug toxicity may occur.

3. Enzyme inhibitors resulting in reduced drug effect

The drugs which are in inactive form at the time of administration is called prodrugs and require patients activation by enzymes in the body before they can produce their effect. Inhibition of the metabolism of prodrugs may reduce the amount of active drug formed, and reduce or eliminate the therapeutic effect.

4. Enzyme induction resulting in reduced drug effect

The drugs which are having capability of increasing the activity of drug metabolizing enzymes is called enzyme inducers, that result in a decrease in the effect of certain other drugs. Drugs metabolized by CYP3A4 or CYP2C9 (CYP-450) are particularly susceptible to enzyme induction. In some cases, especially for drugs that undergo first-pass metabolism by CYP3A4 in the gut wall and liver, the reduction in serum concentrations of the object drug can be profound.

5. Enzyme induction resulting in toxic metabolites

Some drugs are converted to toxic metabolites by drug metabolizing enzymes. Enzyme inducers can increase the formation of the toxic metabolite and increase the risk of hepatotoxicity as well as damage to other organs.

6. Altered renal elimination

For some drugs, active secretion into the renal tubules is an important route of elimination. For example, digoxin is eliminated primarily through renal excretion, and drugs such as amiodarone, clarithromycin, itraconazole, propafenone, and quinidine can inhibit this process. Digoxin toxicity may result.

Pharmacodynamic Interactions

1. Additive Pharmacodyanmic Effects

When two or more drugs with similar pharmacodynamic effects are given, the additive effects may result in excessive response and toxicity. Examples include combinations of drugs that prolong the QTc interval resulting in ventricular arrhythmias, and combining drugs with hyperkalemic effects resulting in hyperkalemia.

2. Antagonistic Pharmacodynamic Effects

Drugs with opposing pharmacodynamic effects may reduce the response to one or both drugs.

Some of the herbs that interact with some drugs that causes the effects

1. Liquorice

Synonym – Yasti, mulethi, glycyrrrhizia.

Biological source – Yasti consists of peeled and unpeeled roots and stolon of Glycyrrhizia glabra. Linn.

Family - Leguminosae.

MOA - Estrogen receptor modulator, testosterone inhibition, antiinflammatory, antiplatelet activity, inhibits carcinogenesis, inhibits P-glycoprotein.

Chemical constituents

- Terpenoid saponin glycyrrhizin.
- Flavonoids (liquiritin, liquiritigenin)
- 20% starch
- 6.5% glucose
- Asparagines
- Carbenoxolone Liquorice

Drugs interacting with liquorice	Type of interaction	Effects of interaction
Nifedipine	Antagonising effect	Hypertention, hypokelamia
Hydrocholthiazide [diuretics], ACE inhibitors	Synergistic effect	Hypokelamia leading to paralysis, cardiac arrest, respiratory arrest, metabolic acidosis
dexamethozone	Synergistic effect	Hypertention, hypokelamia
digoxin	Additive effect	Potentiate the risk of digitalis toxicity, induce hypokalemia, hypernatriemia, edema, hypertension
omeprazole	CYP3A4 induction	Decreased plasma concentrations
midazolam	CYP3A4 induction	Decreased plasma concentrations

Use

- Inhibit H. pylori
- Used to treat leaky gut syndrome.
- Relieve spasmodic cough.
- Mild laxative, diuretic.
- Demulcent Adverse effects & toxicity
- Raise BP- hypertension and oedema
- Prohibited for cirrhosis & gallbladder disease.

2. Cinnamon

Synonym - Kalmi Dalchini.

Biological source – It is the dried of dried inner bark Cinnamomum zeylanicum Linn family -Lauraceae.

Chemical constituents: volatile oil, Coumarin.

Uses

- Diabetes
- Prediabetes
- Obesity
- Premature ejaculation

3. Amla

Synonym - Amlaki, Indian gooseberry.

Biological source - It is the dried and fresh fruits of embilica.

Chemical contituents - Ascorbic acid, tannins.

Uses

- To treat anaemia
- To treat diarrhea
- Prevent jaundice and to treat diabetes
- Used as the immunity booster

Drugs interacting with amla	Type of interaction	Effects of interaction
Metformin	Additive effect	hypoglycemia
Anticoagulant/anti platelet drugs	Additive effect	Bruising or bleeding

4. Ginseng

Synonym - Mans Root.

Biological source - It is the dried of cultivated trees of Korean ginseng (Panex ginseng), South China ginseng (P. notoginseng), and American ginseng (P. quinquefolius).

Chemical constituents

Dammarane derivative: Protopanaxadiols Protopanaxatriols.

Oleanane derivatives: Ginsenoside Ginseng.

Uses

- Memory and thinking skills (cognitive function).
- Erectile dysfunction
- Flu (influenza)
- Fatigue in people with multiple sclerosis
- Increasing response to sexual stimuli in healthy people

Adverse effects & toxicity

- Allergic reaction:
- Hives;
- Difficulty breathing;
- Swelling of your face, lips, tongue, or throat.
- Diarrhea

- Insomnia
- Headache
- Rapid heartbeat
- Increased or decreased blood pressure
- Breast tenderness and vaginal bleeding.

Drugs interacting with	Type of interaction	Effects of interaction
Alcohol	Increased metabolism	Alcohol effects reduce
Caffeine	Synergistic effect	Increased heart rate and high BP
Furosemide	Not known	Decrease effect of furosemide
Aspirin, clopidogrel, heparin, warfarin	Synergistic effect	Enhance brusing and bleeding
Antidiabetic drugs	Synergistic effect	Decrease blood sugar
Phenelzine, tranylcypromine	Synergistic effect	More stimulation

5. Garlic Synonym - allium.

Biological source-It consists of the bulb of the plant Allium sativum.

Family - Liliaceae.

Chemical constituents

- Volatile oils 0.1-0.36%
- Allicin, allin, ajoene.
- Sulphur compounds.
- Allinase enzyme
- Allyl methyl sulphide

MOA

- ❖ Act as a HMG-CoA reductase inhibitor to reduce serum cholesterol.
- ❖ Promote smooth muscle relaxation and vasodilation by activating production of endothelium derived relaxation factor.
- ❖ May have antithrombotic effects leading to decreased platelet aggregation and increased fibrinolytic activity.

Uses

- ➢ Seasoning or condiment.
- ➢ Antibacterial, Antiviral, Antifungal activity and vasodilative effect.
- ➢ Reduce platelet aggregation and hyperlipidemia
- ➢ Regulate blood glucose level.
- ➢ Acne treatment – Antiplatelet.

Adverse effects & toxicity

- Halitosis (bad odor in breath) caused by allyl methyl sulfide.
- Indigestion, nausea, vomiting.
- Increases risk of bleeding.

Drugs interacting with garlic	Type of interaction	Effect of interaction
Ritonavir	Induction of CYP450 3A4 or Glycoprotein transport	Decrease concentration of antiviral
Aspirin	Synergistic effect	Potentiate anticoagulant, antiplatelet inhibition and thrombolytic effects
Warfarin	Synergistic effect	Potentiate anticoagulant, antiplatelet inhibition and thrombolytic
Contraceptive drugs	Increase the breakdown of estrogen	Decrease the effects of contraceptive
Cyclosproine	Induction of CYP450	Decreaseplasma concentration
Saquinavir	p-gp induction	Increase cl and decrease F of saquinavir
Chlorzoxazone	CYP2E1 inhibition	Decrease serum 6-hydroxycholzoxozone

6. Digitalis

Synonym-Foxglove leaves, Dead man's bell.

Biological source- It consists of dried leaves of plant Digitalis purpurea.

Family – Scrophulariaceae.

MOA: Sodium potssium ATPase inhibitor.

Chemical constituents

Digitoxigenin: cardenolide, obtained especially by hydrolysis of digitoxin.Used as a

molecular probe to detect DNA or RNA. Digitalis

Uses

- Useful in patients who remain symptomatic despite proper diuretic and ACE inhibitor treatment.
- Cardiotonic.
- Atrial fibrillation.
- Atrial flutter with rapid ventricular respons.

Adverse drug reaction and toxicity

- Bigeminy (Arrthymia 2 beats occurring in rapid succession) .
- Ventricular tachycardia or fibrillation.
- Increased (atrial) arrhythmogenesis and inhibited atrioventricular conduction.

Common adverse effect

- Xanthopsia. (visual defect-yellow colouration).
- Cause heart block and either bradycardia (decreased heart rate) or tachycardia (increased heart rate.

Driugs interacting with	Type of interaction	Effect of interaction
Betamethazone	Corticosteroid induced sodium and water retention additive effect	Hypokalemia, increase the risk digoxin toxicity, edema leading to heart failure
Glycerin, hydrochlorothaizide	Additive effect	Diuretic induced hypokalemia, hypomagnesimia
Liquorice	Addictive effect	Potentiate the risk of digitalis toxicity, inducedhypokalemia, edema, hypertension
Ramipril	Enzyme inhibitor	Congestive heart failure, renal impairment
St john wort	Enzyme inducer of p glycoprotein	Drecrease the plasma conc of digoxin

Drugs interacting with	Type of interaction	Effects of interaction
Calcium chloride	Additive or synergistic effect	Cardiac arrhythmia
Acebutolol	Additive cardiac effect	bradycardia
Carvedilol, esmolol, talinolol	Enhanced absorption and reduced excretion due to inhibition	Increase in B A of digoxin
Aspirin	Reduced renal clearance of digoxin	Increase plasma digoxin concerntration and half life
Tetracycline	Alter absorption due to changes in intestinal flora	Increase plasma digoxin concentration
Nifedipine	Enzyme inhibitor	Decrease digoxin clearance

7. Turmeric

Synonym-indian saffron, Haldi.

Biological source - It is the dried rhizomes of Curcuma longa.

Family Zingiberaceae

Chemical constituents

- Curcuminoids
- Resins
- Volatile oil

Uses

- Reducing blood cholesterol, reducing osteoarthritis pain Relieving itching .
- Wound healing agent.

Adverse effects & toxicity

- Unusual Bruising Or Bleeding
- Nausea
- Upset Stomach
- Diarrhea or Dizziness
- (high blood sugar-Patients)-increased thirst, increased urination, dry mouth, fruity breath odor,headache)

Drugs interacting with	Type of interaction	Effects of interaction
Anticoagulant/antiplatelet drugs	Synergistic effects	Bruising or bleeding
Tamoxifen,etoposide	CYP3A4 inhibition	Concentration increases
Talinolol	CYP3A2 induction	Concentration decreases
Anti diabetes drugs	Synergistic effect	Blood sugar to go too low
Talazoparib	Increases efflux membrane transporter	Concentration increases

8. Ephedra Synonym -Ma huang.

Biological source - Ephedra consists of the dried aerial parts of Ephedra gerardiana Wall, Ephedra sinica Stapf, Ephedra equisettina Bunge, Ephedra nebrodensis Tineo and other Ephedra species, belonging to family Ephadreace.

MOA- beta-adrenergic agonist.

Chemical constituents

- Ephedrine
- Pseudoephedrine

- Norpseudoephedrine Ephedra

Uses

- Used in bronchial asthma (beta-adrenergic agonist)
- Pre and post spinal anesthesia
- Hypotension
- Stokes-Adams syndrome
- Myasthenia gravis

Adverse effects & toxicity

- Nausea, Headache; dizziness, Decreased appetite
- Irritation of the stomach; diarrhea
- Anxiety; psychosis
- Kidney stones
- Dry mouth
- Irregular or rapid heart rhythms; heart damage
- High blood pressure
- Restlessness; nervousness; sleeping problems
- Flushing; sweating, Increased urination

Drugs interacting with	Type of interaction	Effect of interaction
Phenelzine, tranyleypromine	Additive effect	Fast heartbeat, high BP, seizures, nervousness
Antidiabetic drugs	Antagonistic effect	Decrease the effectiveness of diabetes
Anti convulsants	Antagonistic effect	Decrease the effect

9. Cinchona

Synonym - Jesuit's bark, Peruvian bark.

Biological source - It is the dried bark of cultivated trees of Cinchona officanalis. Linn.

Family – Rubiaceae.

MOA- blood schizonticidal.

Chemical constituents

- Cinchona alkaloids (quinine, cinchonine) -
- Cinchotannic acid.
- Quinic acid.
- Phlobaphene (oxidation product

Uses

- Antimalarial
- Used to treat lupus & arthritis -
- Cutting agent for cocaine and heroin. -
- Regulates heartbeat,
- Stimulates digestion.

Adverse effects & toxicity

- Cardiac events
- Cinchonism
- Hypoglycemia
- Hematological disorders
- Hypersensitive disorder

Drug interacting with	Type of interaction	Effects of the interaction
Rifamycin and cigarette smoking	Enzyme inducers	Increases the elimination of quinine
Amantadine, carbamazepine, digoxin, Phenobarbital, warfarin	Displacement from plasma binding site	Decreases clearance of quinine
Muscle relaxants	unknown	Enhance the effects of quinine
Amiodarone	Additive effect	Prolongation of QT interval
Arsenic trioxide	Additive effect	Prolongation of QT interval
Levomethadyl	Additive effect	Prolongation of QT interval
Anticoagulants	Enzyme inducers	Increases hypothrombinemia

10. St John's wort Synonym: Milleperituis.

Biological source:- This consists of dried aerial parts of the plant known as Hypericum perforatum Linn.

Family:- Hypericaceae.

MOA: SSRI antidepressant (selective serotonin reuptake Inhibitor) St. John's Wort.

Chemical constituents

- Phloroglucinols (Hyperfoirn)
- Naphtodianthrones (Hypericin)
- Flavonoids (Rutin, Quercetin)

Uses

- Antidpressaant
- Seasoning or condiment
- Antibacterial, Antiviral
- Vasodilative effects
- Reduce platelet aggregation and hyperlipidemia.
- Regulate blood glucose level.

Adverse effects & toxicity

- Serotonin syndrome
- Dizziness
- Sedation
- Mania
- Increase in sun sensitivity St. John's Wort.

Drug interaction with	Type of interaction	Effects of interaction
5-HT	Synergistic effect	Serotonin syndrome
Propoxyphene and other CNS depressants	Inhibitor of CYP450 2D6 And synergistic effect	Increase plasma concentration of cns depressants

Ritonavir	Induction of CYP450 3A4	Decrease plasma levels
Chlordiazepoxide	Inhibitor of CYP450 and synergistic effect	Synergistic effect
Levomethadyl acetate	Induction of CYP450 3A4	Risk of qt interval prolongation
Alcohol	Chronic alcoholism results in enzyme induction with acute alcoholism inhibits drug metabolism.	Additive central nervous system depression
Amitriptyline	CYP3A and p-gp induction	Decreased blood concentration of amitriptylin

PATIENT COUSELLING

Herbal formulations are being natural that is being goof for health in public point of view. Here giving awareness about the fact that all the natural extracts are a combination of biologically active compounds that present in unknown quantities.

These herbal products may either have inherent phrmacologcal activity of even show toxicity hereby we would like to share that a survey reprents that 515 users of herbal remedies in united kingdom identified that 30% would consult their physician or general practioner for interactions .clinicians should educate the patients about the herbal medications in non judgemental way. The patient should be cautious for adverse reactions or interactions. The formulation and brand and dose and direction for use of herbal medications should be registered in patient records and monitored regularly. The patients those are having clotting disorders or on anti coagulant therapy should be alerted against the use of herbs like ginkgo, danshen, Dongquai or garlic St. johns wort should be avoided in patients with serotonin reuptake inhibitors, digoxin, cyclosporin, phenprocoumon or any chronic condition Still there is a possibility of unknown interactions.

CONCLUSION

These days mostly people believe the herbal medicine are safe and effective but they are unaware of the interactions and even incidences of mortality and morbidity. Based on many surveys i.e invivo and invitro clinical trials herbal drugs showing many drug interactions. In this article we had focused about various types of interactions like pharmacokinetic and pharmacodynamic interactions, how to get rid of those interactions.

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