Herbal drug interaction and their toxicity

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After completion of session, learner will be able to-

- ✓ Understand mechanisms behind drug interactions
- ✓ Know toxicities and herbal drug interactions of some herbals

Syllabus:

Toxicity in herbals and their interaction: Herbal-Drug & Herbal-Food interactions, General introduction to interaction and classification, Study of following drugs and their possible side effects and interactions

- Hypercium
- kava-kava
- Ginkobiloba
- Ginseng
- Garlic
- Pepper &
- Ephedra

Introduction

- A **drug interaction** is defined as any modification caused by another exogenous chemical (drug, herb or food) in the diagnostic, therapeutic or other action of a drug in or on the body.
- When discussing drug interactions, the drug affected by the interaction is called the “object drug,” and the drug causing the interaction is called the “precipitant drug.”

Mechanism of drug interaction

- divided into two general categories:-

✖ **Pharmacokinetics interaction:-** occur when a herbal changes the absorption, distribution, metabolism, protein binding, or excretion of a drug that results in altered levels of the drug or its metabolites e.g. Liquorice (as an herb, not a sweetener) decreases the metabolism of corticosteroids, leading to adverse and toxic effects from the buildup of corticosteroids

✖ **Pharmacodynamic interactions :-**occur when a herbal product produces additive, synergistic, or antagonist activity in relation to the conventional drug with no change in the plasma concentration of either herbal product or drug. e.g. antagonistic interaction is when an herbal with high caffeine content, such as guarana, is administered with a sedative-hypnotic.

Pharmacokinetic Drug Interactions

❖*Inhibition of Absorption*

Drugs that act as binding agents can impair the bioavailability of other drugs. This will result in a reduction in the therapeutic effect of the object drug. The amount of these drugs that is absorbed from the gut may be increased or decreased by drugs that increase stomach pH.

❖*Enzyme Inhibition Increasing Risk of Toxicity*

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

Since only a few different cytochrome P450 isozymes are involved in drug metabolism, competition between two drugs for these isozymes will occasionally occur. This competition may result in one drug interfering with the metabolism of another drug.

Pharmacokinetic Drug Interactions

•***Enzyme Inhibitors Resulting in Reduced Drug Effect.***

A small number of drugs are not active in the form administered to patients. These drugs are known as prodrugs and require activation by enzymes in the body before they can produce their effect. Inhibition of the metabolism of these prodrugs may reduce the amount of active drug formed, and decrease or eliminate the therapeutic effect.

✖***Enzyme Induction Resulting in Reduced Drug Effect***

Some drugs—called “enzyme inducers”—are capable of increasing the activity of drug metabolizing enzymes, resulting 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 extensive first-pass metabolism by CYP3A4 in the gut wall and liver, the reduction in serum concentrations of the object drug can be profound.

Pharmacokinetic Drug Interactions

➢ ***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.

➢ ***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 Drug Interactions

✖***Additive Pharmacodynamic 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.

✖ ***Antagonistic Pharmacodynamic Effects***

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

St. John's Wort

Synonym :- Hypericum, 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

Drugs interacting with St John's wort	Type of interaction	Effects of the interaction
5-HT	Synergistic effect	Serotonin syndrome
Propoxyphene and other CNS depressants	Inhibitor of CYP450 2D6 and synergistic effect	Increase plasma conc of CNS depressants
Ritonavir (antivirals)	Induction of CYP450 3A4	Decrease plasma levels of antivirals
Chlordiazepoxide	Inhibitor of CYP450 and synergistic effect	Synergistic effect
Levomethadyl Acetate	Induction of CYP450 3A4	Risk of QT interval prolongation and serious ventricular arrhythmias due to increased formation of metabolites
Alcohol	Chronic alcoholism results in enzyme induction while acute alcoholism inhibits drug metabolism.	Additive central nervous system depression
Amitriptyline	CYP3A4 and P-gp induction	Decreased blood concentration of amitriptyline
Atorvastatin	CYP3A4 and P-gp induction	Reduced efficacy of atorvastatin

St. John's Wort

Drugs interacting with St John's wort	Type of interaction	Effects of the interaction
Atorvastatin	CYP3A4 and P-gp induction	Reduced efficacy of atorvastatin
Cyclosporine	CYP3A4 and P-gp induction	Cyclosporine exhibits a relatively small therapeutic window
Digoxin	CYP3A4 and P-gp induction	Decreased blood concentration of digoxin
Methadone	CYP3A4 and P-gp induction	Decreased blood concentration of methadone
Alprazolam	CYP3A4 induction	Decreased blood concentration of alprazolam
Imatinib	CYP3A4 induction	Decreased blood concentration of imatinib
Indinavir	CYP3A4 induction	Decreased blood concentration of indinavir
Irinotecan	CYP3A4 induction	Decreased blood levels of SN-38
Nevirapine	CYP3A4 induction	Decreased blood concentration of nevirapine
Chlorzoxazone	CYP2E1 induction	Increase in hydroxylchlorzoxazone/ chlorzoxazone serum ratio
Bupropion	Additive effects	Orofacial dystonia

Ginseng

Synonym – Man’s Root

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

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.

Ginseng

Drugs interacting with	Type of interaction	Effects of the interaction
Alcohol	Increase metabolism	Alcohol effects reduce
Caffeine	Synergistic effect	increased heart rate and high blood pressure
Furosemide	Not known	Deceases effect of fursemide
Aspirin, clopidogrel heparin, warfarin (**slow blood clotting)**	Synergistic effect	enhances of bruising and bleeding
Antidiabetic drugs	Synergistic effect	decrease blood sugar
Immunosuppressant		
phenelzine (Nardil), tranylcypromine	Synergistic effect	More stimulation

Ginseng

Drugs interacting with Ginseng	Type of interaction	Effects of the interaction
Clozapine Codeine Desipramine Donepezil Fentanyl Flecainide Fluoxetine Ondansetron Olanzapine	Induce Cytochrome P450 2D6	liver breaks down

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

Garlic

Uses

- Seasoning or condiment
- Antibacterial , Antiviral, Antifungal activity
- Vasodilator and has 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.

Garlic

Drugs interacting with Garlic	Type of interaction	Effects of the interaction
Ritonavir	Induction of CYP450 3A4 or p-glycoprotein transport	Decrease plasma conc of antiviral
Aspirin	Synergistic effect	Potentiates anticoagulant, platelet inhibition and thrombolytic effects.
Warfarin	Synergistic effect	Potentiates anticoagulant, platelet inhibition and thrombolytic effects.
Contraceptive drugs	increases the breakdown of estrogen	Decreases the effect of contraceptives
Cyclosporine	Induction of CYP450	Decrease plasma concentration of cyclosporin
Saquinavir	P-gp induction	Increased CL and decreased F of saquinavir
Chlorzoxazone	CYP2E1 inhibition	Decreased serum 6-hydroxychlorzoxazone/ chlorzoxazone ratio

Ephedra

Synonym - Ma huang

B**iological 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

Ephedra

Drugs interacting with ephedra	Type of interaction	Effects of the interaction
Amiodarone , Disopyramide , Dofetilide, Ibutilide, Procainamide, Quinidine, Sotalol, Thioridazine	Synergistic effects	Irregular heartbeat might cause serious side effects including heart attack.
Methylxanthines (Aminophylline, Caffeine, And Theophylline.)	Additive effects	Jitteriness, nervousness, a fast heartbeat, high blood pressure, and anxiety
Diethylpropion, Epinephrine, Phentermine, Pseudoephedrine	Additive effects	Increased heart rate and high blood pressure.
Dexamethasone	Metabolism increases	Decrease the effectiveness of dexamethasone
Ergot Derivatives Bromocriptine, Dihydroergotamine, Ergotamine, And Pergolide	Additive effects	Increase blood pressure too much.

Ephedra

Drugs interacting with ephedra	Type of interaction	Effects of the interaction
Phenelzine, Tranylcypromine,	Additive effects	Fast heartbeat, high blood pressure, seizures, nervousness
Antidiabetes Drugs Glimepiride, Glyburide, Insulin, Pioglitazone, Rosiglitazone, Chlorpropamide, Glipizide, Tolbutamide	Antagonistic effects	Decrease the effectiveness of diabetes medications
Anticonvulsants Phenobarbital, Primidone , Valproic Acid , Gabapentin , Carbamazepine , Phenytoin	Antagonistic effects	Ephedra decrease the effectiveness of medications used to prevent seizures

Liquorice

Synonym - Yasti, Mulethi, Glycyrrhizia.

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

Uses

- Flavourants
- Prevents hyperkalemia.
- 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.

Liquorice

Drugs interacting with liquorice	Type of interaction	Effects of the interaction
Nifedipine	Antagonising effect	Hypertension, hypokalemia
Hydrochlorthiazide (diuretics) and ACE inhibitors	Synergistic effect	Hypokalemia leading to paralysis, cardiac arrest, respiratory arrest, metabolic alkalosis.
Dexamethasone	Synergistic effect	Hypertension, hypokalemia
Digoxin	Additive effect	potentiate the risk of digitalis toxicity, induce hypokalemia, hypernatremia, edema, hypertension, and suppression of the renin-aldosterone system
Omeprazole	CYP3A4 induction	Decreased plasma concentrations of omeprazole
Midazolam (Benzodiazepines)	CYP3A4 induction	Decreased plasma concentrations of midazolam

Liquorice

Drugs interacting with liquorice	Type of interaction	Effects of the interaction
Insulin	Additive effect	Increases side effects of insulin
Laxatives	Additive effect	hypokalemia
Oral contraceptives	Additive effect	hypokalemia
MAO inhibitors	Additive effect	Antidepressant effect
Warfarin (Coumadin)	Displaces warfarin from plasma protein	Increases plasma conc of warfarin

Cinnamon

Synonym – Kalmi Dalchini

B**iological source -** It is the dried of dried inner bark *Cinnamomum zeylanicum* Linn Family -Lauraceae

Chemical constituents -

Volatile oil

Coumarin

Cinnamon

Uses:

- Diabetes
- Prediabetes
- Obesity
- Premature ejaculation

Adverse effects & toxicity

- Liver Damage
- Low Blood Sugar
- Breathing Problems(if inhaled)
- Mouth Sores
- Increased heart rate
- Blood thinner

Cinnamon

Drugs interacting with Cinnamon	Type of interaction	Effects of the interaction
Antidiabetes drugs Limepiride, Glyburide,Insulin, Pioglitazone, Rosiglitazone, Chlorpropamide, Glipizide, Tolbutamide	Synergistic effect	blood sugar to go too low.
Acetaminophen, Carbamazepine, Methotrexate, Methyldopa , Phenytoin		More liver toxicity

Amla

Synonym –Amlaki, Indian gooseberry

B**iological source -** It is the dried and fresh fruits of *Emblica officinalis* Family -Euphorbicaceae

Chemical constituents –

Ascorbic acid

Tannins

Amla

Uses

- Anemia
- Diarrhea
- Jaundice
- Diabetes
- Hypercholestemia
- As an Immunity booster
- In Ayurveda: Amla helps manage indigestion by improving the Pachak Agni (digestion fire). It also helps in easy expulsion of stool due to its Rechana (mild laxative) property.

Adverse effects & toxicity

- Amalaki is rich in fiber, it may lead to gastrointestinal issues, including bloating, stomachache, and diarrhea.
- In addition, it may lower blood sugar, which may cause problems if for people with diabetes

Amla

Drugs interacting with amla	Type of interaction	Effects of the interaction
Metformin	Additive effects	Hypoglycemia
Anticoagulant / Antiplatelet drugs	Additive effects	bruising or bleeding
Acetaminophen, Carbamazepine, Methotrexate, Methyldopa , Phenytoin		More liver toxicity

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 response

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).

Digitalis

Drugs interacting with Digitalis	Type of interaction	Effects of the interaction
Quinidine, Verapamil, and Amiodarone	Displacement from plasma binding site	Increase plasma digoxin levels
Amiodarone	Increase intestinal transit time, reduce renal clearance and volume of distribution, displace digoxin from protein binding sites.	Increase plasma digoxin levels hence additive bradycardia.
Atazanavir	Inhibitor of CYP450 3A4	Prolong the PR interval of the ECG. conduction disturbances and atrioventricular block.
Phenytoin	Enzyme inducer	Decrease plasma digoxin levels-cardiac block

Digitalis

Drugs interacting with Digitalis	Type of interaction	Effects of the interaction
Calcium Chloride	Additive or synergistic inotropic effects of calcium and digitalis glycosides on the myocardium.	cardiac arrhythmias
Acebutolol	Additive cardiac effects	Bradycardia
Carvedilol, Esmolol, and Talinolol	Enhanced absorption and reduced excretion due to inhibition of intestinal and renal P-glycoprotein efflux transporter	increase the B.A of digoxin
Aspirin	Displacement- reduced renal clearance of digoxin.	increase plasma digoxin concentrations and half-life
Tetracycline	Alter absorption due to changes in intestinal flora	increase plasma digoxin concentrations
Nifedipine	Enzyme inhibitor	decrease digoxin clearance increase plasma digoxin levels

Digitalis

Drugs interacting with Digitalis	Type of interaction	Effects of the interaction
Betamethasone	corticosteroid-induced sodium and water retention additive effect	Hypokalemia, increase the risk of digoxin toxicity, edema leading to heart failure
Glycerin (used as diuretic), Hydrochlorothiazide	Additive effect	Diuretic induced hypokalemia,hypomagnesaemia
Liquorice	Additive effect	Potentiate the risk of digitalis toxicity, induce hypokalemia, hypernatremia, edema, hypertension, and suppression of the renin-aldosterone system
Ramipril	Enzyme inhibitor	congestive heart failure (CHF) and renal impairment
St. John's Wort	Enzyme inducer of P-glycoprotein	decrease the plasma concentrations of digoxin

Turmeric

Synonym – Indian saffron, Haldi

B**iological source -** It is the dried rhizomes of *Curcuma longa* Family

Zingiberaceae

Chemical constituents -

Curcuminoids

Resins

Volatile oil

Turmeric

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)

Turmeric

Drugs interacting with turmeric	Type of interaction	Effects of the interaction
Anticoagulant / Antiplatelet drugs	Synergistic effects	bruising or bleeding
Tamoxifen, Paclitaxel, Etoposide	CYP3A4 inhibition	Concentration increases
Talinolol	CYP3A2 induction	Concentration decreases
Antidiabetes drugs Limepiride, Glyburide,Insulin, Pioglitazone, Rosiglitazone, Chlorpropamide, Glipizide, Tolbutamide	Synergistic effect	blood sugar to go too low.
Talazoparib	Increases efflux membrane transporter	Concentration increases

Cinchona

Synonym - Jesuit's bark, Peruvian bark.

B**iological 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)

Cinchona

Usea

- 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

Cinchona

Drugs interacting with liquorice	**Type of interaction**	**Effects of the interaction**
Rifamycins and cigarette smoking	Enzyme inducers	Increases the elimination of quinine
Cimetidine and ketoconazole	Enzyme inhibitors	Decreases clearance of quinine
Amantadine, carbamazepine, Digoxin, Phenobarbital, Warfarin	Displacement from plasma binding site	Serum levels elevated
Muscle relaxants	Unknown	Enhance the effects of quinine
Amiodarone	Additive effect	Prolongation of QT interval
Arsenic trioxide	Additive effect	Prolongation of QT interval
Levomethadyl acetate	Additive effect	Prolongation of QT interval
Anticoagulants oral	Enzyme inhibitors	Increases hypothrombinemia
Antidepressants	Enzyme inhibition	Decreased antidepressant metabolism.
Barbiturates	Enzyme inducers	Increased quinidine metabolism

Thank you