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**HERB-DRUG INTERACTIONS AND TOXICITY: UNDERSCORING  
POTENTIAL MECHANISMS AND FORECASTING CLINICALLY  
RELEVANT INTERACTIONS**

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**ABSTRACT**

Numerous studies have shown that compounds included in traditional herbal medicines may have the ability to change the pharmacokinetics (PK) and/or pharmacodynamics (PD) of pharmaceutical medications. As a result, concurrent use of the conventional medication with traditional herbal remedies may reduce its effectiveness, leading to what are known as herb-drug interactions (HDI). Due of a worldwide dispersed regulatory structure and the inherent heterogeneity of herbal medicine composition; generalizations of such data are contentious.

The World Health Organization (WHO) estimates that between 65 and 80 percent of people in underdeveloped nations rely on medicinal plants for their main healthcare because they are impoverished or do not have access to contemporary medical care. In contrast, herbal medications are widely utilized in the industrialized world because of the widespread notion that they support "healthy living." Given this massive "consumer base," it is anticipated that HDI will have a major negative impact on patients all over the world.

The majority of HDI were discovered either after post-marketing or during clinical interventions, primarily anesthesia. In many nations, including HDI into clinical surveillance is well-established and successful; yet, in others, it is still too costly and/or logistically impractical. Additionally, preclinical evaluation of traditional herbal medications is not

required, despite the fact that it could enhance their safe use and provide information for pharmacovigilance.

The pharmacodynamic and/or pharmacokinetic principles of HDI, the frequency of clinical HDI cases according to national and international records, and the difficulties in identifying them are all covered in this.

**Keywords: Herbal Drugs, P-glycoprotein, Cytochrome P450, Drug design, Drug-Herb Interactions**

## INTRODUCTION:

With sales of about 10 billion dollars in 2019, the use of herbal supplements in the US is a multibillion dollar industry. More than one-third of Americans, according to several polls, report using at least one herbal product and many of those who use them specifically state that using herbals shows independence in managing their own health. Comorbid diseases, pharmacogenomic differences in response and metabolism, and the impact of polypharmacy are some of the complicated aspects that complicate pharmacovigilance for drug–drug interactions. The variety of ingredients in botanicals, misunderstanding brought on by the use of common plant names, incorrect species identification, product labelling, contamination of botanicals, and combination of these factors further complicate phytovigilance for possible herb–drug interactions.

The nature or degree of interaction with pharmacological medicines may change if the botanical product is an extract because the extraction procedure may change its contents. In what has been dubbed "the

entourage effect" in cannabis studies, the entire complement of components in whole plant parts may also affect pharmacodynamics and pharmacokinetics in comparison to extracts. For instance, administering the entire leaf of *Artemisia annua* is said to increase the bioavailability of the anti-malarial component artemisinin by 45 times when compared to administering pure artemisinin alone. Geographical location, genotype, plant part used, and seasonal change all affect a plant.

Species ability to produce different secondary metabolite constituents. The constituent content of crude plants may also be impacted by harvest, processing, and storage.

Information sources about interactions between herbs and drugs might also be difficult. In vitro research findings might provide molecular understanding, but they might not be readily applicable in clinical settings. Though these metabolites may not always be relevant to people and need additional clinical validation, animal models may provide insight into the role of

metabolites in interaction. Sometimes, incorrect plant components or improperly processed products are tested in clinical studies, which are typically conducted in healthy, homogeneous adult populations. Case reports in the literature can provide practical insight into the clinical nature of herb-drug interactions and frequently indicate the need for additional research. However, they can also introduce reporting bias that is skewed toward risk rather than benefit, ignore confounding factors, rarely establish causality, and rarely include perspectives outside the framework of the current medical culture. Interaction checking databases and publications often cite results of clinical studies, in vitro findings, and case reports from the literature. These important clinical tools may reflect risks that lack clinical relevance and may fail to offer insight into combinations that offer benefit. A review published by Ng *et al.* provides an excellent evaluation of sources of herb–drug interaction and adverse effect information [1].

#### **COMMON MECHANISMS OF INTERACTION:**

The patient's state, the medications taken, the administration method, the surroundings, the therapeutic index, and the time of the drug administration all affect the clinical significance of any drug interaction (Kremers, 2002).

The following is a summary of the potential reasons for medication interactions: Competition for absorption through the gastrointestinal tract, binding to transport proteins and plasma proteins, pharmacodynamic interactions at the receptor level, inhibition and induction of metabolism, and competition for active renal excretion.

1. **Enzyme Induction or Inhibition:** Cytochrome P450 enzymes, which are essential for drug metabolism, interact with a variety of herbs. For example, St. John's Wort is known to activate the P450 enzyme system, which may decrease the effectiveness of medications like oral contraceptives and warfarin that are processed by this pathway.
2. **Modification of Drug Absorption:** The gastrointestinal (GI) tract's capacity to absorb medications can be affected by herbs. For instance, some herbs may change the pH of the stomach or speed up the emptying process, which could impact the absorption of drugs.
3. **Protein Binding Interactions:** Herbs have the ability to remove medications from plasma proteins, which raises the blood level of free medicines and may be harmful.
4. **Impact on Renal Clearance:** By influencing kidney function, several herbs can modify the renal clearance of

medications, which can result in modifications to the drug's excretion.

5. **Direct Pharmacodynamic Effects:**

Certain herbs have active ingredients

that either imitate or counteract the pharmacologic effects of prescription medications, producing antagonistic or synergistic effects [2].

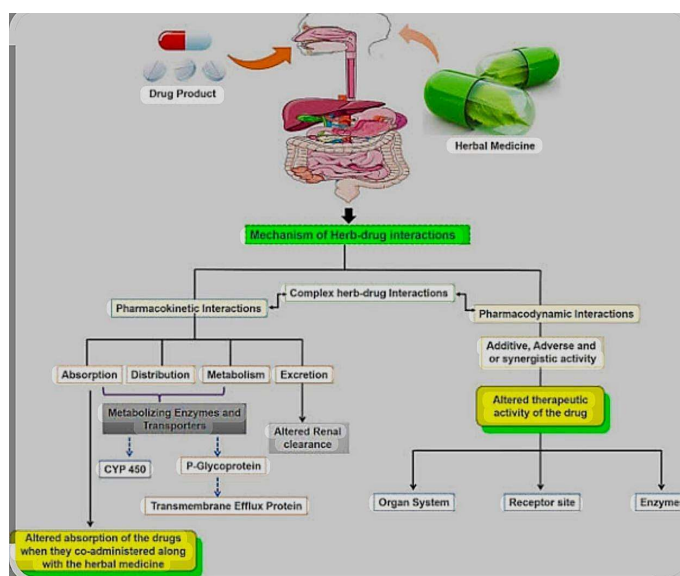


Figure 1: The Therapeutic Significance of Herb-Drug Interactions

**MECHANISMS OF DRUG -HERB INTERACTIONS:**

1. **System of Cytochrome P450**

**Enzymes:**

The cytochrome P450 (CYP450) enzyme system is a key mechanism of drug metabolism, and CYP3A4 is one of the most significant isoforms involved in drug metabolism. Numerous herbs have the ability to either induce or inhibit CYP450 enzyme activity, which can change medication metabolism and result in hazardous or subtherapeutic drug levels [3].

2. **Transporters and P-Glycoprotein:**

Drug absorption and bioavailability may be impacted by interactions between some herbs and drug transporters, such as P-glycoprotein. [4] Drug concentrations in the blood can fluctuate as a result of herbs that either stimulate or inhibit these transporters.

3. **Herbal Influences on the Absorption of Drugs:**

By changing pH, enzyme activity, or gastrointestinal motility, several herbs may have an impact on drug absorption. Ginseng, for instance, has been demonstrated to promote stomach emptying, which may change how

quickly medications taken together are absorbed [5].

#### 4. **Impact on Elimination:**

Herbs may also affect how drugs are eliminated through the liver or kidneys. For instance, it has been demonstrated that St. John's Wort increases the activity of specific hepatic enzymes, which lowers the plasma concentration of medications that are taken together, such as oral contraceptives [6].

#### **Typical Drug-Herb Relationships:**

##### 1. **Herbs that thin the blood and anticoagulants:**

Commonly used herbs like garlic and ginkgo biloba can intensify the anticoagulant effect of blood thinners like warfarin, raising the risk of bleeding [7]. These herbs can increase the anticoagulant effects by preventing platelet aggregation and delaying clotting time.

##### 2. **Both St. John's Wort and antidepressants:**

A popular herb for mild to moderate depression is St. John's Wort. But it triggers the cytochrome P450 system, particularly CYP3A4, which makes medications including immunosuppressants, oral contraceptives, and SSRIs less effective [8].

##### 3. **Statins and Grapefruit Juices:**

Statins like atorvastatin and simvastatin are among the medications whose metabolism is impacted by grapefruit juice's strong CYP3A4 inhibitory effect. Increased medication levels may result from this, raising the possibility of adverse effects such muscle toxicity [9].

##### 4. **Echinacea with Immunosuppressive Agents:**

Although echinacea is used to boost the immune system, it may conflict with medications like cyclosporine that depress the immune system, increasing the chance of transplant rejection [10].

##### 5. **Bitter Melon and Diabetes Drugs:**

Due to its hypoglycemic qualities, bitter melon can raise the risk of hypoglycemia when taken with antidiabetic drugs [11].

#### **Examples of Notable Herb-Drug Interactions:**

##### 1. **St. John's Wort and Antidepressants:**

St. John's Wort is a well-liked herbal treatment for depression, but it can also activate the P-glycoprotein efflux transporter and the cytochrome P450 enzyme system, which lowers the plasma levels of antidepressants like tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). This could result in a decrease in the effectiveness of treatment and a possible recurrence of depression symptoms [12].

2. **Warfarin and Ginseng:** Warfarin and other anticoagulants have been linked to possible interactions with ginseng. Ginseng may increase the risk of clot formation by inducing hepatic enzymes that decrease warfarin's anticoagulant action [13].
3. **Hypertension drugs with Garlic:** Garlic is known to lower blood pressure, and taking it at the same time as hypertension medications may cause excessive blood pressure lowering. This combination may cause symptoms like hypotension, dizziness, and fainting [14].
4. **Immunosuppressive Medications Interactions:** such as cyclosporine may interact with echinacea, which is frequently used to strengthen the immune system. As a result, the immunosuppressive treatment may be less effective, which could jeopardize the results of organ transplants [15].
5. **Statins and Milk Thistle:** Known for its liver-healthy properties, milk thistle may interfere with statins like simvastatin by blocking the cytochrome P450 enzyme CYP3A4, which could raise the statin's blood levels and increase the risk of side effects such muscle toxicity [16].

Table 1: Examples of Herbal Remedies that Interact with Drugs and the Potential Mechanisms

Drug	Herb	Result of interaction	Possible mechanism	Source of evidence	Reference
Alprazolam	St John's wort	Decreased plasma levels Alprazolam	Alprazolam is a specific probe for CYP 3A4, which is induced by St John's wort.	Clinical studies	Jiang et al., 2004, Schmider et al., 2002
Amitriptyline	St John's wort	Decreased plasma levels of the drug	Amitriptyline is a substrate of both CYP2C19 and P-glycoprotein which is induced by St John's wort.	A clinical study	Dannawi et al., 2002
Buspirone	St John's wort	Hypomania	Synergistic effect on 5-HT receptor.	A case report	Gorski et al. 2004
Aspirin	Ginkgo	Spontaneous hyphema	Additive effect on platelet aggregation; ginkgolides show antiplatelet activity	A case report	Leon et al., 1971

**DIFFERENT EXAMPLES OF HERB – DRUG INTERACTION:**  
**HERB -DRUG INTERACTIONS OF PEPPER:**

- Pepper has a diuretic effect; it raises the body's concentration of lithium and reduces its elimination, which can have major negative effects.

- By changing their liver metabolism, it improves the absorption of several medications, including lovastatin, ketoconazole, and ITZ.
- Boosts phenytoin's effects and adverse effects.
- When pepper is added, carbamazepine absorption rises and metabolism falls.
- Piperine makes fexofenadine more bioavailable.
- Piperine reduces the rate at which blood clots. Anticoagulant drugs may thereby increase the risk of bleeding and bruises.
- May intensify phenobarbital's sedative side effects [17].

**HERB-DRUG INTERACTIONS OF GARLIC:**

- Garlic and anticoagulants may lengthen bleeding periods.
- Garlic may cause the liver's CyP3A4 to metabolize protease inhibitors such as indinavir, ritonavir.
- Garlic causes bleeding to occur spontaneously during and after surgery.
- Antihyperglycemic actions are produced when chlorpropamide is taken concurrently.
- Changes in the pharmacokinetics of paracetamol and hypoglycemia are examples of minor interactions.
- Reduces the impact of anti-HIV medications.

- Reduces the effectiveness of calcium channel blockers because to increased hepatic degradation of these drugs [18].

**HERB-DRUG INTERACTIONS OF HYPERICUM:**

- When hypericum and some antidepressant medications mix, an overabundance of serotonin can cause dangerous problems. Confusion, fever, hallucinations, nausea, a lack of muscle coordination, sweating, and shakiness are all signs of this interaction.
- Reduces the effectiveness of the anti-anxiety medication alprazolam by slowing down its metabolism.
- Reduces the effectiveness of birth control tablets.
- Reduces the effects of digoxin, a cardiotonic medication.
- Reduces the effectiveness of anti-HIV medications such as ketamine, irinotecan, and imatinib.
- By inducing CytP3A4, hypericum combined with cyclosporin reduces medication concentration and transplant organ rejection [19].

**HERB-DRUG INTERACTIONS OF EPHEDRA:**

- Ephedra can have major negative effects, including heart attacks, when taken with drugs like amiodarone,

disopyramide, dofetilide, ibutilide, quinidine, etc.

- When combined with methylxanthines, ephedra may result in anxiety, tenseness, rapid heartbeats, and elevated blood pressure.
- Ephedra may cause dexamethasone's effectiveness to decline.
- Reduces the effectiveness of anti-diabetic medications.
- can reduce the effectiveness of anticonvulsant medications like Primidone and phenobarbital [20].

#### **HERB-DRUG INTERACTIONS OF GINSENG:**

- When combined with caffeine, it might result in dangerous side effects like elevated blood pressure and heart rate.
- Reduces the effects of nifedipine, midazolam, furosemide, and estrogen tablets.
- Reduces the effects of medications such as methadone, fluoxetine, fentanyl, donepezil, amitriptyline, clozapine, and imatinib.
- Might lowers the effectiveness of immunosuppressant medicines.
- Blood clotting is slowed by Panax.
- When taken with HIV medications such as raltegravir, ginseng may raise the risk of liver damage [21].

#### **HERB-DRUG INTERACTIONS OF GINKGO:**

- Ginkgo increases the risk of bleeding and bruises when taken with ibuprofen.
- Alprazolam, efavirenz, carisoprodol, citalopram, diazepam, omeprazole, haloperidol, olanzepinepropranolol, etc., can all have their effects lessened.
- Hypomania may result when using it alongside fluoxetine.
- Ginkgo may reduce the rate at which some medications are metabolized.
- Reduce the impact of anti-diabetic medications such rosiglitazone, insulin, glimepiride, etc.
- When used with ginkgo, trazodone can have major adverse consequences.
- When hydrochlorothiazide is taken with ginkgo, blood pressure rises [22].

#### **HERB-DRUG INTERACTIONS OF KAVA:**

- When used with alprazolam, kava makes you drowsy.
- Kava makes you drowsy and interacts with CNS depressants.
- Reduce some medications' hepatic metabolism.
- Etoposide, paclitaxel, vinblastine, vincristine, indinavir, nelfinavir, cimetidine, and corticosteroids are among the drugs that kava improves absorption.
- Hepatotoxicity can occur when kava is taken with medications such

acetaminophen, amiodarone, isoniazid, methyl dopa, itraconazole, etc. [24].

**CLINICAL IMPLICATIONS:**

**1. Diminished Effectiveness of Drugs:**

Certain pharmaceuticals may become less effective when taken with herbal treatments that stimulate enzymes that break down drugs. St. John's Wort, for example, decreases the effectiveness of oral contraceptives, resulting in unintended births [6].

**2. A Higher Chance of Toxicity:**

Medication build-up and toxicity may result from inhibiting medication metabolism, as is the case with grapefruit juice's impact on statins. Rhabdomyolysis and liver damage are among the negative effects that high statin levels might produce [9].

**3. Unexpected Drug Reactions:** Many people don't tell their doctors they take herbal supplements, which might result in undiagnosed and potentially harmful interactions [24].

**Control of Herb-Drug Interactions:**

**1. A THOROUGH MEDICAL HISTORY:**

It is essential that medical professionals have a complete history of any herbal supplements that patients have taken. This makes it easier to spot possible interactions and lessens the chance of negative outcomes.

**2. MONITORING DRUG LEVEL:**

When patients are taking prescription drugs and herbal supplements, it is crucial to regularly monitor drug levels and clinical outcomes, particularly for those having a narrow therapeutic index (e.g., digoxin, warfarin) [25].

**3. UTILIZING DATABASES OF DRUG INTERACTION:**

Healthcare professionals can find possible drug-herbal product interactions by using clinical decision support systems and drug interaction databases (such as Medscape and Lexicomp) [26].

**4. PATIENT EDUCATION:**

It is crucial to inform patients about the dangers of taking prescription drugs along with botanicals. Prior to starting herbal supplements, patients should be advised of the possibility of adverse effects, changes in drug efficacy, and the necessity of speaking with their healthcare practice [27].

**INITIAL RECOGNITION OF POSSIBLE HERB-DRUG INTERACTIONS:**

• **CASE REPORT:**

The first signs of potential herb-drug interactions are frequently case reports that are published in the peer-reviewed medical literature. Although case reports typically aren't able to prove causation,

they can help create ideas for potential mechanisms.

- **ADVERSE EVENT REPORTS (AERs):** Many AERs recorded to the FDA's MedWatch program may be related to herb-drug interactions.
- **IN VITRO SCREENINGS:** Impacts of phytochemicals on isolated cell lines expressing human drug-metabolizing enzymes or transporters or on purified enzymes and transporters.
- **PROSPECTIVE IN VIVO STUDIES:** Use human participants to evaluate the diverse impacts of botanicals [28].

#### **SIGNIFICANCE TO STUDY HERBAL-DRUG INTERACTIONS:**

- Health and treatment effectiveness may be impacted by herbal medication interactions, as certain herbal remedies may.
- Increases pharmacological adverse effects, which can result in toxicity.
- Results in treatment failure since the medications' effects diminish.
- Changes in pharmacological action may result in unforeseen problems.
- Increase the drug's therapeutic effect.
- Prescription and over-the-counter medications can change how the body responds to herbal treatments [29].

#### **CONCLUSION:**

In clinical practice, drug-herb interactions are a complicated and important issue.

Healthcare providers need to be on the lookout for potential hazards and advantages of herbal products, especially when they are used in conjunction with prescription drugs. It is essential to inform patients about the dangers of using herbs for self-medication in order to avoid negative consequences and guarantee safe and efficient treatment regimens.

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