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HERB-DRUG INTERACTIONS: MECHANISM AND MITIGATION STRATEGIES

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ABSTRACT
Herb-drug interactions (HDIs) are crucial in healthcare due to the growing popularity of combining herbal supplements with traditional medications. These interactions can alter drug effectiveness or increase toxicity through pharmacokinetic and pharmacodynamic pathways. Pharmacokinetic HDIs involve changes to drug-metabolizing enzymes and transporters, affecting absorption, distribution, metabolism, and elimination. Conversely, pharmacodynamic HDIs occur when herbs interact with drug targets, impacting therapeutic outcomes. To manage HDIs, a holistic approach is vital, requiring thorough patient assessments, provider knowledge, patient education, reference to reliable sources, and regulatory support for informed decision-making.

KEYWORDS: Herb-Drug Interactions (HDIs), Pharmacokinetics, Pharmacodynamics, Risk Education.

INTRODUCTION

Herb-drug interactions occur when a conventional medicine taken concurrently with an herbal component may change the drug's pharmacological effects, or vice versa. The outcome of the herb-drug interaction could be increased or decreased in the effects of the drug or herb, or it could result in the emergence of a new effect not expected from using the drug or herb alone. It happens after the patient takes the medication and herbs simultaneously.[1] The interaction between the herbs and drug or vice versa are occur due to increase in consumption of herbal supplements along with the drug without informing healthcare professional. Millions of Indians regularly utilize over-the-counter (OTC) herbal medications as self-medication in addition to using them as spices, home cures, and health foods.[2] The majority of herbal medications have negative effects on patients when used with allopathic medications. Given its abundance of natural resources, traditional medical knowledge, and history of using plants as medicine, India is a very medicinally advanced country. Of the 1,500 therapeutic plants recognized by the Indian medical system, 500 are regularly utilized. Over 7800 pharmaceutical production facilities are thought to exist in India, and these facilities are thought to use about 2000 tons of herbs a year. The World Health Organization (WHO) recently estimated that 70–80% of the world's population, particularly in developing nations, gets their main healthcare from traditional medicine, which primarily uses plant-based medications. The growing popularity of herbal remedies calls for attention to the interactions between herbal remedies and allopathic medications. The growing popularity of herbal remedies calls for careful consideration and examination of the interactions between herbal remedies and allopathic medications. Combining certain herbal supplements with prescription medications can have potentially harmful side effects. Patients suffer more when utilizing alternative therapy since it is typically used unsupervised by doctors or other alternative therapy professionals. This is particularly true if patients combine prescription and herbal medications, which may have unintended interactions. These encounters may go unreported until a patient suffers harm or until a major, potentially fatal incident has place.[3] From ancient Indian use herbs for their treatment but consumption of herbs along with Allopathic drug without consulting healthcare professional may cause potential effects as mentioned above. As herbal drug is not having side effects and available at low cost as compared to Allopathic medicine hence the use of herbal medicine is expanding quickly, raising worries about possible herb-drug interactions.

Mechanism

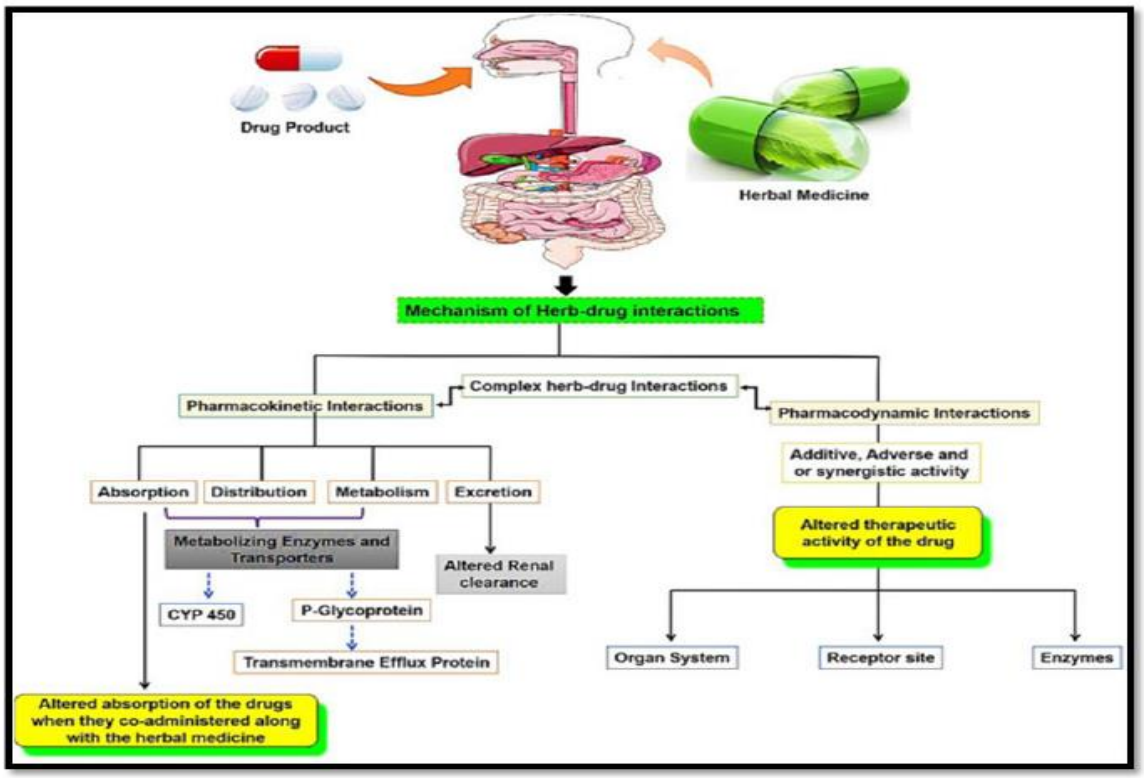


Figure no. 1: Mechanism of herb drug interaction.

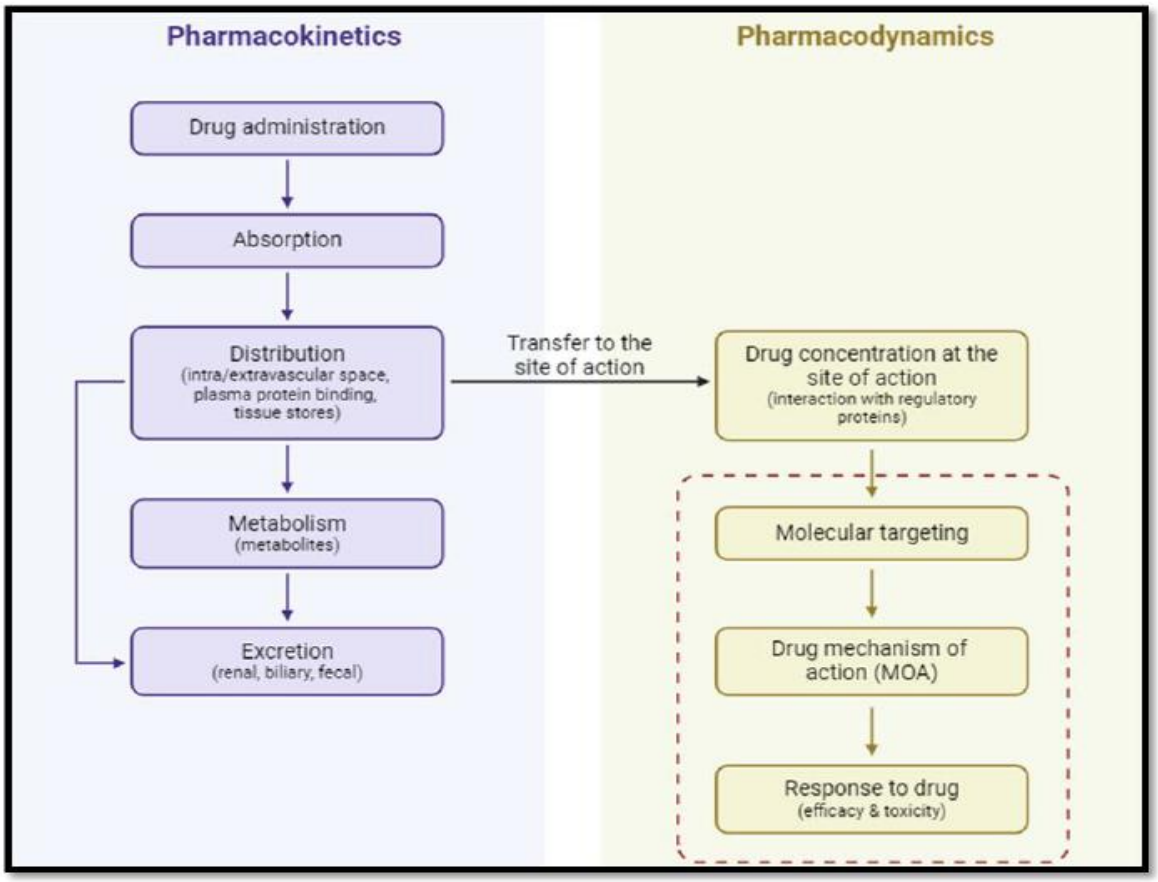
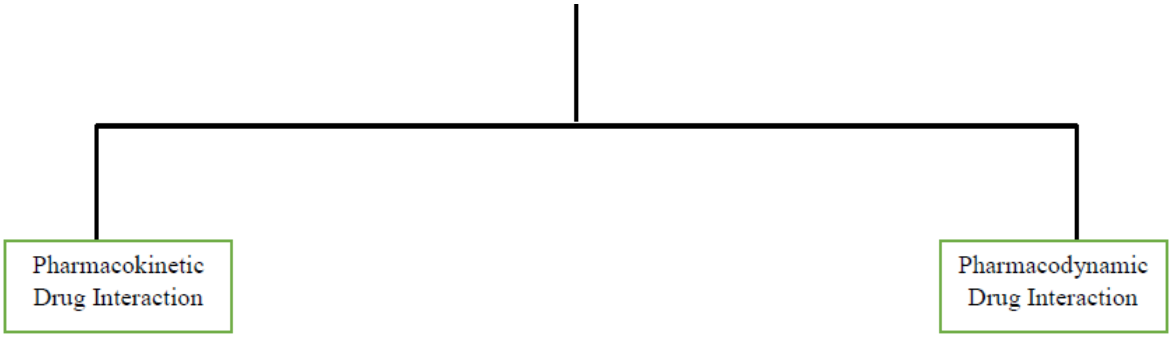


Figure no. 2: Basics of Pharmacokinetic and Pharmacodynamic.

The concurrent use of medicinal drugs and herbs often raises the possibility of pharmacokinetic or pharmacodynamic interactions. Research indicates that various herb-drug interactions can alter the efficacy of medications and lead to adverse effects.[6] There are two primary categories of herb-drug interactions: Pharmacokinetic and Pharmacodynamic.



A. Pharmacokinetic drug interaction

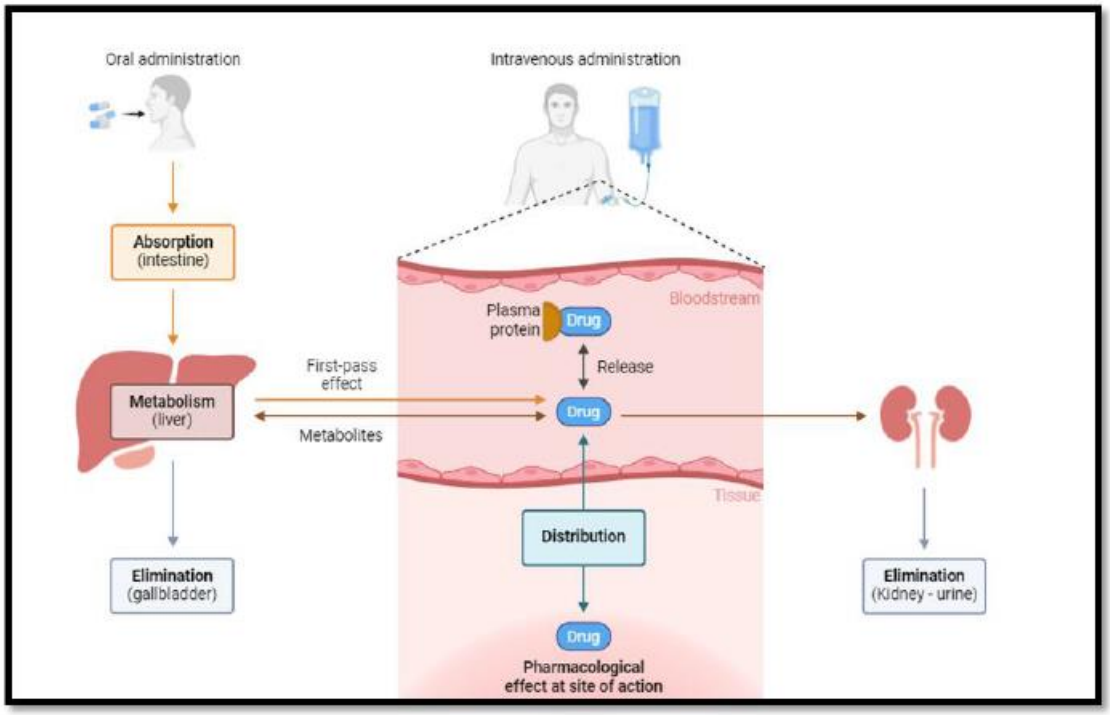


Figure no. 3: Pharmacokinetic drug interaction.

The alterations in the absorption, metabolism, distribution, and excretion of drugs are responsible for pharmacokinetic interactions between herbs and pharmaceuticals. A common mechanism behind the changes in drug concentrations due to the use of herbal products is the stimulation or inhibition of hepatic and intestinal cytochrome P-450 enzymes (Segal & Yu, 2010).

Herbal medicines can interfere with the normal functioning of drug transporters through either competitive or non-competitive mechanisms, leading to pharmacokinetic interactions. Furthermore, these interactions may also occur due to the upregulation of mRNA for specific proteins, resulting in increased production of transport proteins. Research has identified several therapeutically relevant P-Glycoprotein inhibitors, including phytochemicals such as flavonoids, furanocoumarins, reserpine, quinidine, yohimbine, vincristine, and vinblastine.[7]

The amount of a medication that reaches systemic circulation and its site of action are critical in determining both its therapeutic effects and adverse drug reactions (ADRs). These elements are shaped by the drug's pharmacokinetics, which include bioavailability, metabolism, distribution, and clearance, as well as the dosage and method of administration. Data from preclinical and clinical pharmacokinetic studies, along with the benefit-risk ratio—an assessment of the drug's long-term safety and effectiveness highlight various factors such as age, disease conditions, genetic

variations, and polypharmacy that can influence pharmacokinetics and, in turn, the drug's effects. Additionally, the concurrent use of herbal medicines may contribute to a drug's ineffectiveness or lead to unexpected side effects. Specifically, components of herbal extracts can modify the pharmacokinetics of pharmaceuticals, potentially causing toxicity or inadequate therapeutic outcomes if the drug achieves excessively high or insufficient tissue concentrations. Understanding whether the constituents of a medicinal plant can activate or inhibit transporters or metabolic enzymes may help predict potential pharmacokinetic interactions between herbal products and conventional medications. Consequently, numerous in vitro studies have investigated whether specific herbal extracts or their components can stimulate or inhibit transporters or drug-metabolizing enzymes, particularly cytochrome P450 (CYP450) isoforms and P-glycoprotein (P-gp). Furthermore, plant constituents may also interact with phase I and II enzymes, as well as transporters from the ATP-binding cassette (ABC) and solute carrier (SLC) families.[8]

The absorption, distribution, metabolism, and excretion (ADME) of therapeutic drugs are significantly influenced by proteins and enzymes that are essential for drug transport.

Concept of P – Glycoprotein: P-Glycoprotein, which originates from the term "permeability-glycoprotein" and is also referred to as multidrug resistance protein 1, belongs to the superfamily of ABC transporters. This protein has been extensively researched due to its essential functions, which include:

1) Facilitating drug efflux by actively transporting a variety of toxins, xenobiotics, and other compounds out of cells, thereby safeguarding the organism from harmful substances;
2) Serving as a protective barrier that prevents many substances from penetrating the brain, a function associated with the Blood-Brain Barrier.

Often termed the Cellular Gatekeeper, P-Glycoprotein plays a significant role in regulating the absorption, distribution, metabolism, and excretion (ADME) of therapeutic drugs. Additionally, certain herbs can interact with the binding sites of P-Glycoprotein, potentially modifying the activity of therapeutic drugs and leading to harmful drug interactions.[9,10]

The interaction of HDI within metabolic processes- Pharmacokinetics herb-drug interactions during metabolism occur when the concurrent use of herbal products and medications either enhances or suppresses the activity of metabolizing enzymes due to the ingestion of therapeutic drugs alongside herbs. For instance, the activation of metabolizing enzymes, particularly CYP enzymes, can often result in therapeutic failure as it leads to diminished plasma concentrations of the drug. A notable example is St. John's Wort (Hypericum perforatum), which is known to stimulate CYP3A4 and CYP2B6, thereby reducing the plasma levels of chemotherapy agents such as irinotecan and imatinib. Generally, the inhibition of CYP enzymes tends to elevate the plasma levels of the co-administered drug, potentially increasing its toxicity. Furano coumarins, such as naringenin and bergamottin found in Paradiso juice and C. sinensis, have been shown to raise the plasma concentrations of various medications, including cyclosporine, terfenadine, midazolam, and felodipine, both in vitro and in vivo, by acting as 'suicide substrates' for the CYP3A4 enzyme. Additionally, certain plants like meadowsweet and black willow, which contain salicylates that alleviate pain, may displace highly protein-bound drugs such as warfarin and carbamazepine, thereby intensifying the adverse effects associated with these treatments.[11]

Sr no	Herbs	Herb - Drug Interaction	References
1	Ginger	The concurrent use of ginger with cyclosporine significantly reduced the bioavailability of cyclosporine.	Chiang et al., 2006
2	Turmeric	Turmeric has been shown to lower the expression of UGT UDP-glucuronosyltransferases during the metabolism of indapamide and xipamide, leading to conditions such as hyponatremia and hypokalemia.	Prieto-Garcia et al., 2023
3	Green tea	Green tea enhances the peak concentration (Cmax) of simvastatin by inhibiting the CYP450 3A4 enzyme, which may elevate its levels in the body and increase the risk of myopathy.	Surana et al., 2021
4	Garlic	When saquinavir is combined with garlic, there is an increase in the expression of the metabolic enzyme cytochrome P450 (CYP3A4), which is part of P-Glycoprotein. This interaction results in a significant increase in the clearance of saquinavir and a decrease in its bioavailability.	[15]
5	St. John wort	Numerous studies involving humans have highlighted the effectiveness of St. John's wort (Hypericum perforatum) in inducing CYP3A4 and P-Glycoprotein, leading to decreased effectiveness of various medications, including oral contraceptives, digoxin, venlafaxine, cyclosporine (Sand immune), tacrolimus, warfarin, protease inhibitors, and irinotecan (Camptosar).	[16]

B. Pharmacodynamic drug interaction

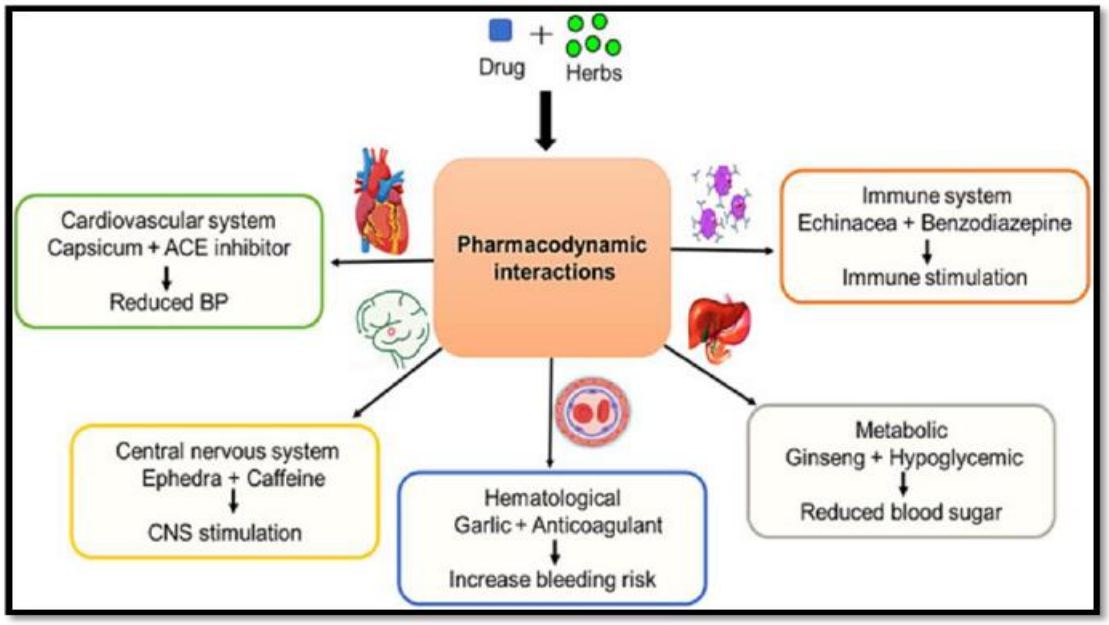


Figure no. 4: Pharmacodynamic drug interaction.

Pharmacodynamic interactions involving medicinal herbs lead to alterations in pharmacological responses, which can manifest as changes in a drug's physiological effects and mechanisms of action within the body, as well as modifications in the relationship between drug concentration and its effects. These interactions can either enhance or inhibit the pharmacological activity of a concurrently administered drug. Consequently, any changes in a drug's pharmacological effects whether through additive, synergistic, or antagonistic mechanisms—are classified as herb-drug pharmacodynamic interactions. A significant concern arises from the fact that a single herbal preparation may contain various components, each potentially possessing unknown biological activities. This complexity allows an herbal remedy to either replicate, amplify, or diminish the effects of other drugs by targeting the same biological pathways simultaneously. If the interaction results in a synergistic or additive enhancement of the drug's effects, it may lead to adverse outcomes, including target organ toxicity, as evidenced in clinical cases involving the anticoagulant warfarin. Conversely, some herbal remedies may contain antagonistic compounds that reduce the pharmacological effectiveness of medications, potentially leading to therapeutic failures, as seen with statin therapies. Thus, the co-administration of herbal remedies and pharmaceuticals can result in either synergistic or antagonistic effects due to their competition for the same pharmacological targets.[21] The fundamental aspect of pharmacodynamics involves the receptor.

Sr no	Herbs	Herb - Drug Interaction	References
1	Caffeine	Caffeine and ephedrine are both stimulants, and their combined use can result in significant adverse effects, such as elevated heart rate, increased blood pressure, and potential long-term cardiovascular issues.	(Belayneh & Molla, 2020)
2	Garlic and Ginger	The simultaneous use of garlic or ginger with anticoagulant medications can inhibit the metabolism of anticoagulants like warfarin, resulting in elevated blood concentrations of these drugs and a heightened risk of bleeding.	Macan et al., 2006
3	Ginko biloba	The use of warfarin can lead to severe bleeding, particularly when combined with Ginkgo biloba and aspirin in elderly patients experiencing hemorrhage in the anterior chamber of the eye.	[18]
4	Kava	The intake of kava, which contains Kavalactones, alongside central nervous system depressants can amplify the effects of these depressants, including barbiturates and benzodiazepines.	Anke et al., 2004
5	Piperine	Combining Piperine with antidepressants such as sertraline HCL can enhance the interactions between the two, thereby increasing the efficacy of the antidepressant treatment.	[20]

Clinical importance

Herb-drug interactions play a vital role in clinical practice, as they can greatly affect the safety and efficacy of prescribed medications, particularly for patients who use herbal supplements alongside conventional treatments. For example, herbal remedies like St. John's Wort (Hypericum perforatum) can reduce the effectiveness of drugs such as oral contraceptives and immunosuppressants by activating the cytochrome P450 (CYP3A4) enzyme.[30] On the other hand, herbs like ginkgo biloba and ginseng may enhance the effects of anticoagulants such as warfarin, increasing the risk of bleeding. These interactions can lead to therapeutic failures, adverse reactions, or even serious health issues. Populations at greater risk include the elderly, individuals with chronic illnesses, and those taking multiple medications, due to alterations in pharmacokinetics and the common use of both drugs and supplements. Therefore, it is essential for healthcare providers to assess the use of herbal products and be alert to potential interactions, as ignorance or failure to report such usage can have significant clinical consequences. Establishing clinical guidelines and pharmacovigilance strategies is essential for the effective detection and management of these interactions.[31]

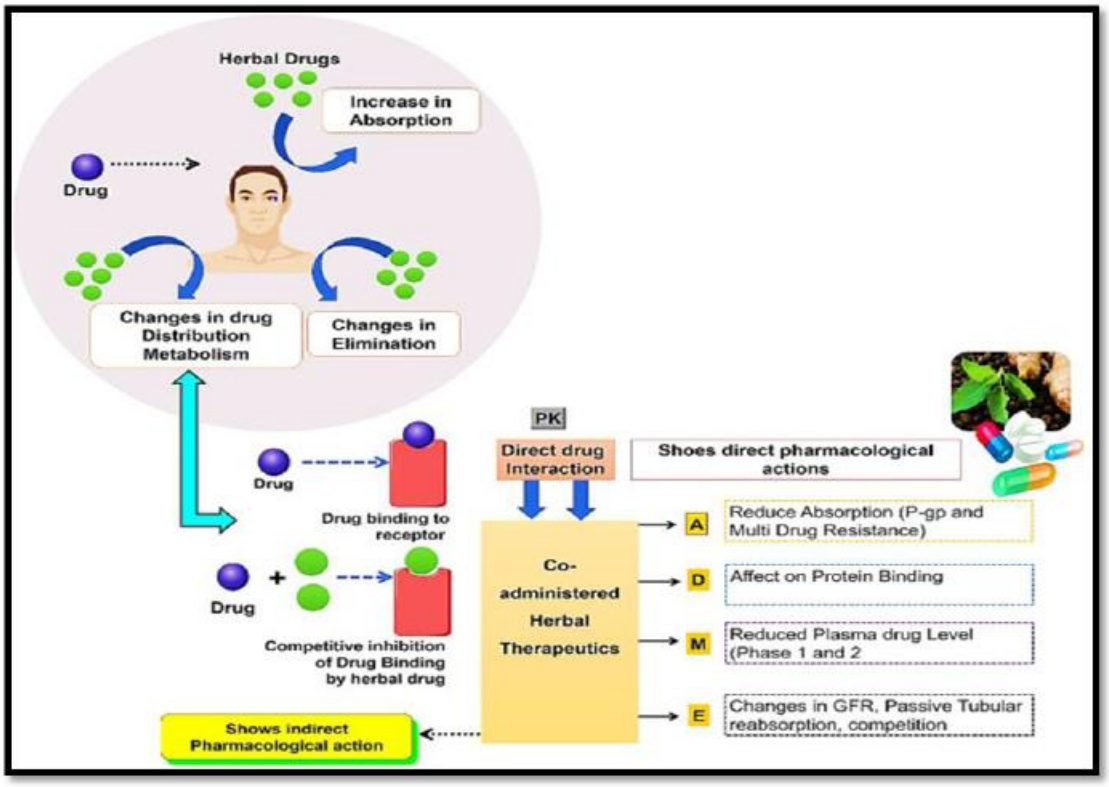


Figure no. 5: Clinical importance of drug herb interaction.

Strategies for preventing herbs-drug interaction

1) **Herbo vigilance –** The existing pharmacovigilance framework requires a comprehensive redesign to address the unique characteristics of herbal medicines in contrast to conventional pharmaceuticals, as it is predominantly tailored for modern drugs. Alternatively, a new system could be developed, termed "Herbo vigilance," which would focus on the safety of herbal products, their interactions with contemporary medications, and the various factors influencing these interactions, including pharmacodynamic and pharmacokinetic aspects and their underlying mechanisms. This communication encompasses signal detection and other activities typically associated with the pharmacovigilance system.[22]

2) **Age -** Older adults are at a higher risk of experiencing interactions between herbs and medications due to alterations in their physiological processes, particularly in renal and hepatic detoxification and clearance. Furthermore, this age group may face challenges in metabolizing medications effectively.[23]

3) **Polypharmacy -** Polypharmacy, which is increasingly prevalent among the elderly, is a significant contributor to herb-drug interactions. This term refers to the concurrent use of multiple medications to manage various health conditions, a practice that is becoming a growing concern for older adults. Individuals in this age group often suffer from multiple chronic conditions (MCCs), characterized by the presence of more than one long-term illness, including but not limited to depression,

diabetes, hypertension, asthma, arthritis, and chronic obstructive pulmonary disease. The likelihood of drug interactions escalates in the elderly due to polypharmacy. In multicentre European studies involving 1,601 older participants in randomized controlled trials, 46% exhibited potential drug-drug interactions. Other research indicates similar rates of interaction among senior patients, ranging from 35% to 60%. Alarmingly, the incidence of drug-drug interactions can approach 100% when the number of medications increases significantly. Therefore, it is crucial to minimize polypharmacy (Rombolà et al., 2020).

4) **Route of administration –** The administration pathways for both natural products and pharmaceuticals warrant careful examination. In clinical settings, herbal remedies are predominantly taken orally, leading to potential interactions mediated by intestinal metabolism when drugs are also administered via the oral route. Specifically, the interactions between herbs and drugs in the intestinal environment are of significant clinical relevance and merit further exploration, given the abundance of metabolizing enzymes and transporters present in the intestine.

For instance, orally ingested Ginkgo biloba leaf extracts influence the pharmacokinetics (ADME: Absorption, Distribution, Metabolism, and Excretion) of nifedipine only when it is taken orally, as opposed to when it is administered intravenously.

Similarly, Zingiber officinale root juice diminishes the oral bioavailability of cyclosporine, while having no impact on the pharmacokinetics of intravenous cyclosporine. This phenomenon may be linked to the herb's effects on metabolic enzymes in both the liver and the intestine.

Therefore, when prescribing both medications and herbal products to patients, it is crucial for physicians to consider the route of administration to mitigate the risk of adverse effects stemming from herb-drug interactions.[24]

5) **Engagement with a healthcare professional -** Notify your healthcare provider of all prescription and over-the-counter medications you are currently using or plan to use. Additionally, inform your healthcare professional about any vitamins, dietary supplements, and herbal products you are taking. It is also important to disclose any other medical conditions you may have, such as hypertension or diabetes.

When receiving a prescription from your physician or obtaining a drug or herbal product from your pharmacist, be sure to ask the following questions:

i) Are there any potential drug interactions I should be aware of?
ii) What signs should I look for, that may indicate medication interactions?[25]

6) **Steering clear of herbal dietary supplements when taking medication -** Estimates indicate that between 20% and 25% of individuals using prescription medications also incorporate dietary supplements into their routines, with a notable 40% to 60% of Americans suffering from chronic conditions doing the same. This trend has raised significant concerns regarding the potential interactions between dietary supplements, especially herbal ones, and prescription drugs. The National Centre for Complementary and Integrative Health categorizes dietary supplements as a diverse range of products, including probiotics, vitamins, minerals, and herbs.[26]

Herbal Supplements	Uses	Interaction between drug and Supplement	References
Milk thistle	Reduce the presence of amyloid plaques in the brains of animals affected by Alzheimer's disease while protecting the liver from harmful pollutants. Additionally, improve cancer treatment and support acne management.	The concentration of drugs such as diazepam, phenytoin, and warfarin, which are metabolized by CYP2C9, may be diminished.	[27]
St John wort	Reduction of hot flashes and other symptoms associated with menopause. Utilized for the treatment of insomnia. It aids in promoting wound healing and managing nerve pain or neuralgia.	The effectiveness of oral contraceptives, digoxin, tacrolimus, warfarin, cyclosporine, and certain over-the-counter medications may be reduced.	[28]

Herbal remedies refer to supplements specifically designed for internal use. Many over-the-counter and prescription medications are derived from plant sources. What distinguishes these products is their use of FDA-regulated purified substances, unlike natural supplements. However, the FDA does not oversee the manufacturing of herbal supplements, leading to variations in quality and the potential inclusion of either parts or the whole plant. While they can be found in liquid or powder forms, herbal supplements are

predominantly available in solid forms such as capsules, pills, tablets, and lozenges. This analysis focuses on the common health issues addressed by widely used herbal supplements in the United States, highlighting the importance of the interprofessional team in managing patients who utilize these products.[27]

CONCLUSION

Drug-herb interactions pose significant risks to patient safety, especially as the concurrent use of herbal supplements and conventional medications becomes more common. These interactions can lead to changes in drug efficacy, heightened toxicity, or unexpected side effects. They frequently arise from the impact of herbal ingredients on drug metabolism, particularly through enzymes like cytochrome P450 or transporters such as P-glycoprotein, which can either enhance or reduce the effectiveness of medications. To address these interactions, a comprehensive approach is essential, which involves educating both healthcare professionals and patients about the potential risks, encouraging transparent conversations about the use of herbal supplements, and applying evidence-based strategies for risk assessment. Regulatory bodies should enforce stricter quality control and labelling standards for herbal products to ensure that consumers have access to accurate information. Ultimately, improving education, fostering clinical vigilance, and advancing research on herb-drug interactions are vital for minimizing adverse effects and protecting patient safety in a landscape marked by increasing polypharmacy and the use of herbal remedies.

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