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Review Article

Herbal medicines and drug interactions: A growing concern in healthcare

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Abstract

The widespread use of herbal remedies worldwide, frequently in combination with traditional pharmaceuticals, raises questions regarding possible drug-herb interactions. These interactions can result in changed pharmacological efficacy, increased toxicity, or negative effects when the active ingredients in herbs modify the pharmacokinetics or pharmacodynamics of prescription medications. Modification of enzyme that metabolize drug (such as cytochrome P450 enzymes) and transporter of drug For example P-glycoprotein) are common mechanisms of herbal-drug interactions. These processes can either improve or hinder the ADME (absorption, distribution, metabolism, or excretion) of pharmaceuticals. It has been demonstrated that common herbal remedies used for treatments such as, ginkgo biloba, ginseng, garlic, and St. John's Wort interact with a variety of prescription drugs, such as immunosuppressants, anticoagulants, antidepressants, and antiretrovirals. Certain interactions may decrease the therapeutic efficacy of medications, which poses concerns, particularly in populations with chronic disorders like diabetes or cardiovascular diseases, while other interactions may result in significant clinical effects. In order to improve patient safety, the abstract highlights important case studies, investigates the pharmacological underpinnings of herbal drug interactions, and stresses the significance of incorporating knowledge regarding herbal use into clinical practice. In the expanding field of complementary and integrative medicine, reducing dangers and maximizing therapeutic results require greater knowledge, patient education, and systematic research on herbal supplements and how they interact with medications.

Keywords: Herbal Medicines, Drug Interactions, Healthcare

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1. Introduction

"According to the World Health Organization, herbal remedies are defined as finished, labelled pharmaceutical products that contain plant parts, airborne substances, or preparations derived from plants, whether in their raw form or as processed materials, or mixtures there of". Juices, gums, fatty oils, essential oils, and any other similar things are considered to be plant material. Excipients may be added to herbal remedies in addition to the pharmaceutical active ingredients. The growing prevalence of herbal medical products (HMPs) in communities where prescription drugs are also widely used raises the possibility of serious public health consequences from unfavourable herb-drug interactions. Herb-drug interactions have been identified by regulatory bodies around the world, including the Therapeutic Goods Administration, U.S. Food and Drug Administration, Medicines Control Agency, and the Medical Products Agency, as a significant safety concern.11 A lot of prescription medications and herbal remedies can be hazardous at certain doses while being beneficial at others. The pharmacological or toxicological effects of each constituent can be altered by the interaction of herbs and drugs. The synergistic therapeutic effects of long-term medications may make their administration more challenging. For example, herbs have historically been used to lower blood glucose levels in diabetics.22 could potentially cause hypoglycemia if combined with traditional medications.

Herbal medications are widely used, but the scarcity of reported side effects and interactions is likely attributed to two factors: underreporting and the generally safe nature of

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the herbs commonly used. In the realm of herb-drug interactions, there is a dearth of experimental evidence, case reports are few, and case series are uncommon. "There is also a lack of data on drug-drug interactions, as most clinical studies on this topic are limited to case reports. Randomized controlled trials are scarce due to ethical concerns about intentionally assigning patients to studies that investigate potential adverse effects." Although significant, the actual frequency of medication interactions is unknown. A study of 1000 senior patients admitted to the hospital from the emergency room revealed alarming rates of drug-drug interactions. Specifically, 538 patients (53.8%) experienced a total of 1087 drug-drug interactions, and notably, 30 patients (5.6% of those with interactions) suffered adverse effects as a direct result of these interactions.3 As of right now, the primary alternate method for carrying out research on Herbal Drugs is gathering real-world evidence through observational research. The data used to compile this proof came from actual sources such administrative claims databases, medical records, and polls. Real-world studies, especially those conducted at the population level, enable researchers to investigate the effects of herb-drug combinations outside of controlled settings, despite significant constraints. 4 Observational studies are essential to fill in this knowledge gap by providing accurate data on the application, safety, and efficacy of HMs as well as investigating any potential therapeutic implications of any interactions with conventional medications. In order to assess the usefulness of practical data analysis in observational research examining the clinical implications of concurrent use of HMs and conventional drugs, this review article set out to address the lack of a comprehensive review that concentrates on real-world evidence of positive or negative effects from the combined use of HMs and conventional drugs in prior literature. This was primarily achieved by providing clarification on the selected data sources and study methodologies as well as by indicating potential directions for more research.5

2. Mechanism of Action of Herbal Drug Interaction

Drug-herb interaction is same as pharmacokinetic and pharmacodynamics drug-drug interaction.

2.1 Pharmacokinetic interaction

It involves Absorption, Distribution, Metabolism, Elimination of drug molecule.

1. **Absorption:** Absorption which means, The process by which a drug moves from the administration site into the bloodstream. Herbal medication and drugs when administered by oral route they absorbed into blood through the gastrointestinal route i.e stomach and intestine. The herbal constituents may alter the physiochemical environment of the stomach and intestine such as changes in intestinal pH, complexing mechanism and intestinal motility which leads to changes in concentration of drug that enters into the bloodstream.6[6] For example, common ingredient in herbal weight loss product are laxative herbal constituents such as Aloe vera leaf, Guar gum and Senna, which may results in the decrease in the intestinal transit time and reduction of drug absorption. Mucilage and gum are water soluble but poorly absorbable.7[7] The psyllium, rhubarb, flaxseed, marshmallow, and aloe are the gum and mucilage containing plants that can bind to other various types of drugs and reduce their action E.g. the absorption of lithium is inhibited by psyllium rhubarb and Aloe vera can cause diarrhoea, which results in reduction of their action of drugs having the narrow therapeutic index. It can be avoided by taking the drugs one hour before or two hours after consumption of herbal medicaments.7[7]

2. **Distribution:** Distribution means, The process by which a drug moves from the bloodstream to its target site in the body. Herbal constituents such as Meadowsweet and Black willow can bind to plasma proteins and contain pain-reducing salicylates. These herbs have ability to dislocate highly protein bounded drugs such as carbamazepine and warfarin and increases serum drug levels. Thus, adverse effects of these drugs are enhanced when taken concurrently.8[8]

3. **Metabolism:** The process by which the body breaks down a drug into a new form, called a metabolite. Upon entering the bloodstream, drugs undergo metabolism in the liver, where they are either converted into their active therapeutic forms or broken down and eliminated from the body. Herbal drugs have the ability to alter hepatic metabolism by induction or inhibition of liver enzymes. Thus, herbal medicament can alter the count of therapeutically active drugs by two ways: Enzyme Induction activity: the herbs has activity to stimulate the production and the activity of enzymes leading to degradation and elimination of drugs residue from the plasma. It decreases the amount of drugs e. g St. John's Wort as it induces the activity of the cytochrome P450 enzymes. It could lower the concentration of warfarin, digoxin, protease inhibitors, theophylline, carbamazepine, etc., or the effectiveness of oral contraceptives. The enzyme needed to break down the medicine may be inhibited by herbs, which would raise the drug's levels. While enzyme inhibition might happen in two to three days, the process of enzyme induction can take days or weeks. It causes toxicity to develop quickly. For instance, licorice reduces the metabolism of corticosteroids, which can have harmful and toxic effects. According to an in vitro investigation, cytochrome P450 and the isoenzyme CYP3A4 may be inhibited by herbs such as chamomile and echinacea. Combining medications such as simvastin, alprazolam, calcium-channel

blockers, and protease inhibitors may result in negative side effects and elevated serum drug levels. P-glycoprotein and cytochrome p450 enzyme play crucial role in drug metabolism and transport, affecting drug absorption, distribution, and elimination. Such as P-glycoprotein is an ATP-binding cassette (ABC) transporter found in various tissues including intestine, liver, kidney and blood-brain barrier. And Cytochrome P450 (CYP) Enzyme are a family of heme-containing enzymes primarily found in the liver and intestine responsible for the metabolism of many drugs.9,10[9,10]

4. **Elimination:** Elimination is the process by which the body removes a drug from the body. Few number of drugs are excreted through the renal route. The herbal medicaments may alter the renal functioning and may influse the drug level in the blood. The drug level found in blood may increase, if the herbal medicaments reduces renal function, while it may decrease if the herb increases its renal functioning. The serum drugs levels are affected due to changes in excretion. E.g Chronic licorice consumption can interfere with antihypertensive and antiarrhythmic medications by causing hypokalaemia and water retention.11,12[11,12]

2.2 Pharmacodynamic interaction

Pharmacodynamic interactions occur when two or more substances (e.g., herbs, medications) affect the same biological pathway or mechanism, resulting in an altered response.1,13[1,13]

2.3 Additive interaction

Herbs can have an impact that is comparable to that of drugs and can intensify their effects. Therefore, using herbal sedatives, anticoagulants, and antihypertensive at the same time as prescription medications may enhance their effects.[13-15] Combined effects of two substances, resulting in a response that is the sum of their individual effects.

2.4 Antagonistic interactions

This indicates that the herb may have the opposite effect of the drug, minimizing the effects of the treatment. For example, ephedra and other herbs high in caffeine, such as cola nut, guarana, mate, and green tea, which are frequently used in weight-loss products, may oppose the effects of antihypertensive medications.16,17[16,17]

2.5 Synergistic

The desired effect of the drugs is enhanced when used together. For example, a combination of antihypertensives can be prescribed to reduce blood pressure.

3. Interaction of Herb and Drug

Table 1: Interaction of herbs with antibiotics, cardiac glycoside, and antihypertensive medicines.

Herbs	Synonyms	Antibiotics	Interaction Outcome	Reference
Eleuthero	Devil's bush	Monomycin, Kanamycin	↑Effects of antibiotics.	33
Guar Gum	Stabiliser Guaran	Penicillin V	Herb slows the absorption in the stomach.	34
Milk Thistle, ubiquinone(co-enzymeQ10)	Holy thistle	Doxorubicin	risk of thrombotic complications in warfarin-treated patients. Decrease cardiac side effects from medication to decrease kidney toxicity of herb.	19
Digitalis	Digitalin Digitalis glycoside	Erythromycin	Erythromycin can raise serum levels of digitalis glycosides, which can enhance both the therapeutic effects and adverse effects.	21 22
Piperine	Piper nigrum Piperin	Propranolol	↑C max and AUC.	18
Guggul	Indian bedellium	B-blockers and calcium channel blockers	↓efficacy of beta blockers and calcium blockers.	29
Aloe	Aloe barbadensis	Thiazide diuretics	Due to electrolyte imbalance increase cardiac toxicity.	29
Senna	Cassia Augustifolia	Amlodipine, Metoprolol.	Herbs may decrease potassium (K) levels.	29

4. Other Antihypertensive Medicines Interact with Herbs

4.1 Ephedra

This strong decongestant, which contains ephinephrine, effectively widens bronchial passageways, but its potent stimulant properties can cause sleeplessness, elevated blood pressure, and other adverse effects, making it a contentious substance that should be avoided when taking cardiac medications or receiving treatment for glaucoma, thyroid issues, or hypertension.[22]

4.2 Ginseng

This supplement is often adopted to help lower cholesterol, increase energy, improve stamina, and reduce stress. However, it can elicit feelings of anxiety and excitement, and excessive use may result in adverse effects such as headaches, sleeplessness, and palpitations. Additionally, it can raise blood pressure levels. Therefore, it is not recommended for individuals taking coumarin or high blood pressure medication.[23]

4.3 Licorice

Used to cure stomach ulcers, colds, and coughs. Excessive dosages may cause potassium loss, water retention, and elevated blood pressure. Use caution while taking digoxin or diuretics together since this may induce further potassium loss, which is detrimental to heart health.[25]

4.4 Cayenne Pepper

Reports of potential interactions between antihypertensive medication, which lowers blood pressure, and MAO

inhibitors. When taken in excess, may harm the kidneys and liver.[26]

Table 2: Interaction of herbs with cardiac glycosides

Herb	Synonyms	Interact with Drug	Interaction outcome	Reference
zSt. John's Wort	Hypericum pyramidatum	Omeprazole, Cyclosporine	↓AUC by25% and CMax trough by 26% (through P- glycoprotein induction).	26-27
	Hypericum maculatum	Tacrolimus	↓Area Under Curve by57.8%.	26,29
		Alprazolam, Atorvastatin	Reduce concentration.	
		Nifedipine (Calcium channel blocker)	Nifedipine: C max ↓38.5%, area undercurve decrease 44.9%, Dehydronifedine: Cmax increase 55.9%, area under curve (AUC) increase 25.7%.	
Siberian Ginseng	Eleutharo		Increase concentration of digoxin.	33
Licorice	Glycyrrhiza glabra	Potassium-depleting Diuretics	Decrease efficacy and increase digoxin side effects (large doses decrease K, low K and hence risk for digitals toxicity).	19
		Diuretics	Decrease toxicity of diuretics (large doses ↓K).	
Guar gum	Guaran		Absorption of digoxin in stomach is slow.	29
Indian Snakeroot	Rauwolfia trifoliate		Herb can increase effect.	33
Plantain	Rock rose		Herb may disrupt the kinetics and monitoring of absorption.	29,34

Table 3: Interaction of herbs with corticosteroids and NSAIDs

Herb	Synonyms	Interact with Drug	Interaction outcome	Reference
Licorice	Glycyrrhiza glabra	Sotalol	Enhance corticosteroids. Increasing blood pressure by licorice and decreasing the effect of sotalol	28,19
Echinacea	Coneflowers	Cyclosporine	Echinacea potentiates the immune system and decreases cyclosporine effect	26,27
Ginseng (American)	Ginseng panax	Aspirin Metformin Clopidogrel Furosemide	Possible synergic interaction with aspirin and increasing the risk of bleeding and may have additive effects or affect the concentration of steroids.	26,32

		Heparin Warfarin		
Turmeric	Curcuma launga curcumin	Doxorubicin	Synergistic effect on cancerous cell and cardiomyocytes	[51]
Ginkgo	Ginkgo biloba	Aspirin Clopidogrel Heparin Enoxaparin Warfarin	Increasing the risk of bleeding.	[26,31]
Garlic	Allium sativum	Acetaminophen Indomethacin Platelet inhibitors	Increased sulphation through induction of enzymes. ↑indomethacin level. Increased bleeding tendency,Platelet dysfunction, Haemorrhage	[52,53]
Feverfew	Chrysanthemum parthenium	NSAIDs Aggregating agents	May ↓therapeutic effect of feverfew. Platelet dysfunction and platelet antagonism	
Green Tea	Hyson	Sulindac and /or tamoxifen warfarin	Synergistic effect. decreased response to warfarin.	[19]

4.5 Implication of drugs that interact with herbs in drug development

Anticipating drug interactions with herbal supplements is difficult for drug scientists because of the general dearth of knowledge describing their pharmacologic activities and composition.[35] Current understanding suggests that many herbal remedies must not be taken at the same time with many other drugs that are substrates for cytochrome P3A4 and P-glycoprotein. The dramatic increase in the use of herbal medicine worldwide means that many more patients on conventional medicines are being exposed to herbal medicines, so it is important to identify drugs in a timely manner that can interact with herbs. These drug interactions could pose a safety risk to drug scientists.

There is little information available about who is using these products and for what purposes since they are unwilling or do not believe it is necessary to disclose to clinicians the kinds and dosages of herbal treatments being used.[36] Because of this, drug interactions with herbal remedies are probably more common than drug-drug interactions and are very likely to be greatly underreported and undervalued. The oxidative metabolism of more than 50% of currently prescribed pharmaceuticals involves CYP3A4, therefore herbal medicines that activate this enzyme are likely to interact with a much greater number of medications than previously known.[35] Only a very tiny percentage of currently marketed medications have been looked at for possible interactions with human botanicals like ginkgo and St. John's wort. Therefore, more carefully thought-out clinical research is undoubtedly needed to learn more about how drugs interact with herbs. The crucial study of interactions between herbs and medications depends on the ability to accurately detect the presence of altered anabolysem and transport, as well as the ability to measure the level of inter-mutualism and its scientific significance in drug development. The creation of novel compounds that are categorised as "strong drugs," or those that are not transported by P-gp or cytochrome-Ps, is one possible tactic to resolve undesirable drug interactions with herbal remedies.[40] Ariens was the one who originally put up the idea of "hard drugs."[36] These medications have easy kinetics of excretion through the kidney or bile because they are non-metabolizable. Their pharmacokinetics are therefore straightforward and typically predictable. There will be much less chance of interactions when these medications are used in conjunction with natural medicines. If medications must be taken in addition to herbal therapies, there are situations in which reasonable drug usage is required. This establish utilizing a safe protocol for combining drugs, modifying dosages, and discontinuing therapy when detrimental interactions occur between drugs and herbs. When used with drugs that enable continuous evaluation of plasma drug concentrations and related toxicities, herbs with limited pharmacological index are recommended.

5. Risks Associated With Herb-Drug Interactions

Drug interactions typically result in a wide range of outcomes, from serious side effects that cause the patient little concern to treatment failure, potentially deadly adverse effects, or even death.[36] Regretfully, anecdotal data from misquoted published papers and misunderstandings has led to irrational inferences being made about the potential hazards associated with several herbal treatments. A case in point is the coumarin-containing herb Melilotus officinalis, also referred to as sweet clover. Initially, it was thought that the coumarin content of this herb caused bleeding disorders.

But it was eventually found that dicoumarol, a molecule produced from coumarin by bacteria in hay that had been destroyed, was the cause of the illness. Sweet clover loses its anticoagulant properties when it is thoroughly dried because it does not contain dicoumarol.[38] Even when the insufficient reporting of side effect in the herbal industry is given into account, well-documented and credible examples of harm caused by the use of herbal medicines continue to be extremely few. However, there are safety concerns related to herbal medications that should be properly evaluated in light of reliable information.[39] The inclusion of a distinct system for classifying the safety of herbal medicines, which primarily addresses pharmacokinetic herb-drug interactions, The significance of these interactions in assessing the safety of herbal products is emphasized in the second edition of the Botanical Safety Handbook by the American Herbal Product Association. When a therapeutic plasma level is raised above the maximum hazardous concentration or when its drug plasma level is not reached, the pharmacokinetic herb-drug interaction's severity is typically determined by these two factors. Patients who use medications with limited therapeutic windows are more vulnerable since even slight variations in the blood levels of these medications might have harmful side effects or fail to produce the desired results. Furthermore, while using herbal remedies in addition to prescription medications, some circumstances and diseases could necessitate routine patient monitoring. The most susceptible patient groups are those receiving treatment with medications with low therapeutic indexes (such as theophylline, phenytoin, phenobarbital, warfarin, immunosuppressive drugs, digoxin, and certain anti-retroviral drugs.), patients with impaired hepatic and renal function, old person, new-borns, new mothers, organ transplant recipients, and those with specific genetic disease.[33] Some individuals are in particular need of additional and alternative therapies to either treat their conditions or lessen the adverse side effects of traditional medicines. Cancer patients are more susceptible in this sense because, compared to the general population, they take complementary and alternative treatments more frequently.[1,2] When undergoing chemotherapy, some cancer patients take up to eight herbal supplements.[40] Poly pharmacy and complementary therapies, especially herbal remedies, are commonly linked. There is a higher chance of interactions when patients use multiple allopathic medications (polypharmacy) in addition to natural medications (occasionally many herbal medications).[41] Based on proven cases and clinical studies, it is interesting to note that only a small fraction of regularly used herbal medications are contraindicated for usage when used in combination with allopathic drugs when taken in normal doses.[42] In recent years, a number of reliable, scientifically supported sources have emerged to categorize herbal remedies according to how safe they are to take in addition to prescription medication .[3,43–45] Under "Interaction Checker," there is a search feature that offers the most recent data on interactions between over-the-counter and prescription medications and herbs.[46]

6. Limitation of Herb-Drug Interaction

Case reports provide the majority of the information that is currently available regarding the interactions between herbal medicines and prescription medications. But now, clinical research is also starting to show up in the literature. Given that causality is rarely proven beyond a reasonable doubt, even case reports with documentation should be regarded with caution. In accordance with the Fugh-Berman and Ernst scoring system, 68.5% of the reported cases were classified as "unevaluable" (meaning that there was not enough information in the reports to determine the likelihood of an interaction), 18.5% as "possible" (meaning that the reports suggested an interaction but there might have been other factors contributing to the event), and 13% as "well documented" (meaning that the reports seemed to offer solid evidence for an interaction).[37]

7. Misidentification, Adulteration, and Contamination

The composition of herbal items may not always be fully disclosed on their labels, and negative responses or interactions linked to particular herbs may really be the result of mislabelled plants, prescription medications, or heavy metals.[47] Examining a "Siberian ginseng" (Eleutherococcus senticosus) product associated with a case of neonatal androgenization, for example, turned out to be Chinese silk vine (Periploca sepium), an unrelated species.[43] Empathy and neuropathy linked to a Chinese herbal remedy allegedly prepared from long-dan-cao (Gentiana rigescens) roots in Hong Kong were demonstrated to be brought on by Podophyllum emodi, a distinct plant. 56- Guangfang-ji (Aristolochia fangchi), a weight-loss supplement, was actually the source of more than 48 cases of renal toxicity that were reported to fang-ji (Stephania detrandra). Erythrolochic acid is known to be a nephrotoxin.[48] In the latter instance, the Chinese names' similarity appears to have caused the error. The mix of medications and "herbal" goods is an issue with Chinese patent medications. Two-thirds of the 2609 traditional Chinese medicine samples that were taken from eight Taiwanese hospitals contained pharmaceutical adulterants, the most common of which were caffeine, paracetamol, indomethacin, hydrochlorothiazide, and prednisolone.[49,50] Non-steroidal anti-inflammatory medicines (NSAIDs) and benzodiazepines are included in several Chinese prescription medications that are distributed outside of Asia; Among these substances are Chuifong Toukuwan, Tung Shueh, and Miracle Herb. A number of formulations have been available since 1974; these include aminopyrine, hydrochlorothiazide, phenylbutazone, indomethacin, diazepam, diclofenac, mefenamic acid, and dexamethasone. The latter formulation is the most well-known. Heavy metal contamination is common in Asian herbal products. In California, USA, herbal shops yielded a

total of 251 Asian patent medications with lead (at least 1 ppm), arsenic, and mercury.[50]

8. Conclusion

With ramifications for both medicine and the economy, phytopharmaceuticals, or herbal medicine, are a subject of growing international interest. Most people agree that herbal medications are secure and efficient treatments. Because they think plant medicines have no negative side effects, people are therefore turning more and more to herbal medicine. On the other hand, medicinal plants may be hazardous on their own or in conjunction with other medicines. The adverse effects of herbal medicines can vary in severity, causing mild to severe side effects such as rashes and allergic responses, headaches, nausea, vomiting, and diarrhoea. Research indicates that there may be harmful side effects from herbal medications. According to a study, certain users of herbal medicines may have liver damage and kidney failure as a result of the dangerous interactions they have with other medications or the presence of heavy metals or toxic compounds.

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10. Conflict of Interest

None.

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