Journal of Medicinal Natural Products

Scilight

Review

Herb-Drug Interactions: A Critical Exploration in Modern Healthcare Practices

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Received: 10 March 2025; Revised: 28 April 2025; Accepted: 30 May 2025; Published: 3 June 2025

Abstracts: Herb-drug interactions (HDIs) are a growing concern in modern healthcare, with almost 70% of individuals using herbal remedies alongside conventional pharmaceuticals. These interactions can have either beneficial or adverse consequences, and the concentration of a medicine in a certain tissue may change due to these interactions. Herb-mediated blockage and activation of protein transporters and drug-metabolizing enzymes, such as the CYP450 framework, is a common method that pharmaceuticals and herbs collaborate on. Herbovigilance, is the surveillance and assurance of the responsible use of conventional drugs, is crucial for the safety of herbal treatments. However, the frequency of adverse pharmacological reactions associated with herbal treatments has been refuted by numerous scientific studies. Herbal molecules can interact with medicines via pharmacodynamic pathways, leading to antagonistic, combined, and synergistic effects. The quality of herbal remedies is another significant risk factor, as it is difficult to precisely evaluate the safety and efficacy of herbal remedies due to problems like adulteration, misidentification, and contamination. Unpredictable therapeutic effects and an elevated risk of interaction can also result from variations in the content of herbal products, often caused by variations in production and preparation techniques. Despite the increasing awareness of the importance of monitoring HDIs, there is still a lack of standardized guidelines for assessing HDIs, leading to unreported adverse reactions and underestimated risks of using traditional and herbal remedies simultaneously.

Keywords: herb-drug interactions; modern healthcare; pharmacokinetics; herbal drugs; interactions; conventional drugs

1. Introduction

Herb-drug interactions (HDIs) are a significant issue with the increasing use of herbal treatments around the world. When a plant and a drug are taken together, certain interactions can happen and have either beneficial or adverse consequences [1,2]. All over the world, almost 70% of individuals take herbal remedies in addition to or instead of conventional pharmaceuticals. The increasing popularity of herbal remedies may be attributed to its perceived safety, affordability, and ease of use [3]. Whereas varying concentrations of active phytochemicals in herbal remedies may alter several physiological functions, including carriers and enzymatic systems. It is established that these compounds have pharmacological activity [4]. Herb-mediated blockage and activation of protein transporters as well as drug-metabolizing enzymes, that generally include the CYP450 framework, is a quite common method that pharmaceuticals and herbs collaborate [3,4]. The concentration of a medicine in a certain tissue may change because of these interactions, which could have a detrimental effect on medicine metabolism. A wide range of interaction found in accessible sources are hypothetical or dependent on unreliable information, and there are relatively few comprehensive studies assessing the interactions between prescription drugs and herbal products. But this topic must be taken into consideration because certain medications, such as warfarin, digoxin, and chemotherapy therapies, have a therapeutic index that is relatively small [5]. HDIs are a developing concern due to the increased usage of herbal medicines worldwide. Sufficient clinical data are needed

to assist with making well-informed decisions about patient safety to maximize clinical results and reduce the adverse effects of herbs while minimizing potential interactions [3].

2. Mechanisms of HDIs

The pharmacokinetic and pharmacodynamic routes may result in interactions between herbs and drugs [4,6]. When most of herbal extracts change how a medicine is absorbed, distributed, metabolized, and eliminated, this is referred to as a pharmacokinetic interaction [4,7]. Drug interactions between medications are often mediated by drug-metabolizing enzymes, particularly those belonging to the cytochrome P450 (CYP) enzyme family, or drug-carrying proteins such as P-glycoprotein (P-gp) [6,8]. Ashwagandha (*Withania somnifera*) possesses synergistic effects and increases CYP3A4 activity. It provides protection to the liver and blood cells against drug-induced harm when taken in conjunction with ritonavir. Moreover, it may intensify the sedative effects of drugs include clonazepam, diazepam, or lorazepam if administered with benzodiazepines [9]. Garlic (*Allium sativum*) activates the CYP3A4 enzyme, which can decrease drugs metabolism. Moreover, it inhibits P-glycoprotein (P-gP) and CYP2C9. Consequently, a decrease in Saquinavir metabolism may lead to adverse medication responses, a higher risk of bleeding while taking Warfarin, and a decrease in docetaxel clearance [10]. Ginkgo (*Ginkgo biloba*) suppresses the activity of the liver enzyme CYP2C9, it significantly reduces the metabolism of many drugs, such as tamoxifen, celecoxib, glipizide, tolbutamide, and piroxicam. When evaluating patient treatment alternatives, this interaction needs to be considered [11]. Grapefruit juice (*Citrus* × *paradisi*), inhibits CYP1A2, CYP3A4, and CYP2C9, three enzymes involved in drug metabolism. This inhibition may result in higher blood levels of different drugs, which could have harmful effects and be hazardous. People on drugs including saquinavir, acyclovir, lovastatin, atorvastatin, nifedipine, amiodarone, clomipramine, and carbamazepine should be aware that grapefruit juice can raise blood levels of these drugs. The safe and efficient administration of treatment regimens depend on knowledge of these interactions [12]. Kava (*Piper methysticum*), Pineapple bromelain (*Ananas comosus*), and Saw palmetto (*Serenoa repens*) all induce the CYP2C9 enzyme, that substantially reduces the efficacy of warfarin, a vital anticoagulant. While utilizing these medications together with warfarin, take caution and seek advice from a medical professional [13,14]. Liquorice (*Glycyrrhiza glabra*) includes Glycyrrhizin, an 11-keto steroid that can inhibit CYP 2C9 and 3A4 activation and mimic corticosteroid effects. Warfarin and lidocaine suppress activities, whereas corticosteroids increase actions through synergistic. The effects of spirolactone are amplified [15]. Peppermint (*Mentha piperita* L.) has a capability to suppress CYP3A4, that could enhance Felodipine's efficacy. Additional research concerning the combination use of these medications to maximize treatment outcomes is made possible by this interaction [16]. Pippali (*Piper longum*) inhibits the enzymes CYP3A4, CYP2D6, and CYP1A2. Essential drugs including digoxin, propranolol, and verapamil are substantially less efficient because of this inhibition. It is essential to take these interactions into account while prescribing or using these medicines [17]. St. John's wort (*Hypericum perforatum*) can activate CYP1A2, which improves the metabolism of several medicines. Moreover, it stimulates P-glycoprotein (P-gP) and CYP3A4. Therefore, the efficiency of cyclosporine may be reduced when used with warfarin and its anticoagulant effects, protease inhibitors, and atorvastatin. To maximize patient care and avoid possible problems such transplant graft rejection, it is essential to comprehend these relationships [18]. Tulsi (*Ocimum sanctum*), contains active ingredients such as linalool, carvacrol, and eugenol that efficiently block the CYP1A1 and CYP1B1 enzymes. This inhibition is essential because it stops the procarcinogen benzo[a]pyrene from becoming the extremely toxic diolepoxide. Since the liver's CYP1A1 and CYP1B1 are primarily responsible for the conversion process, inhibiting them is an important defense mechanism. It is crucial to recognize that extended exposure to diolepoxide may result in unfavorable dermatological effects, including as thickening, darkening, and pimple development [19,20]. Turmeric (*Curcuma longa*) substantially inhibit the enzyme activity of CYP3A4, CYP1A2, CYP2B6, CYP2C19, and CYP2C9, the efficacy of rosuvastatin, warfarin, clopidogrel, and losartan is certainly reduced [17]. Aloe vera (*Aloe barbadensis miller*) shall be administered with precaution because it may cause hypokalemia whenever utilized together with diuretics or corticosteroids. In these circumstances, potassium levels should be checked to assure safe and efficient use [21]. Amla (*Emblica officinalis*) is well-known for containing a high tannin content that can bind with iron. Although ascorbic acid breaks down at high temperatures, it is frequently advised to take raw amla powder. Amla is also known for its high calcium concentration. Raw amla powder ingestion may reduce iron levels and perhaps reduce the potency of iron tonics. It is also vital to understand that an excessive consumption of amla might lead to the formation of renal stones [22]. Coffee (*Coffea arabica*) and Tea (*Camellia sinensis*) both substantially enhance stomach acidity. The efficiency of antibiotics including erythromycin and penicillin is impacted directly by this rise, which leads to their degradation. Limiting the intake of these drinks during antibiotic treatment is essential for the best outcomes [23,24]. Flax seeds (*Linum usitatissimum*), Marshmallow (*Althea officinalis*), and Aloe vera

(*Aloe barbadensis miller*) might decrease the absorption of certain drugs in the body. The substantial mucilage content of these plants may prevent the absorption of drugs [25]. Ginger (*Zingiber officinalis*) inhibits thromboxane synthetase, that could prolong bleeding time. When using ginger with anticoagulant drugs like warfarin, care should be taken because this combination may increase the risk of severe bleeding. For using ginger in nutritional and medicinal applications, it is crucial to comprehend this possible interaction [13]. Passion flower (*Passiflora incarnata*) possesses additive effects, which substantially increase the efficacy of central nervous system (CNS) depressants [26]. Pomegranate (*Punica granatum*), Tomato (*Solanum lycopersicum*), composed of melatonin, and sweet flag (*Acorus calamus*) has significance because of their potent combined actions. These herbs are a potent combination for managing epilepsy since they absolutely amplify the anti-epileptic effects of carbamazepine when taken with it [27]. Purple coneflower (*Echinacea purpurea*) & Coneflower (*Echinacea angustifolia*) possess prominent antagonistic effects. Echinacea's immunostimulant effects can significantly decrease the effectiveness of immunosuppressive drugs [4]. Sugandhbala (*V. wallichi*) & Garden heliotrope (*Valeriana officinalis*) possess a synergistic action that substantially boosts the efficacy of central nervous system depressants [28]. Herbal phytoconstituents can interact with medicines via pharmacodynamic pathways, that include the medications' receptors or biological processes, and lead to antagonistic, combined, as well as synergistic effects [4,6]. Herbal treatments typically contain multiple active substances that may interact with one another to achieve distinct therapeutic goals. As a result, there is a higher chance of potentially major HDIs than there is with medication interactions [6]. It is challenging to forecast the quantity and therapeutic significance of these interactions due to the complicated composition of herbal extracts and the dearth of clinical data [3,7]. It is necessary to carefully monitor any possible interactions, particularly in high-risk patients who are taking drugs with limited therapeutic indices or in people who have long-term illnesses that call for several prescriptions [3].

3. HDIs and Herbovigilance

Herbal products have the potential to change the pharmacokinetics of traditional medicines, resulting in HDIs serious pharmacological complications (Figure 1). They typically occur when components found in herbal medicines have an impact on transporters or enzymes that metabolize drugs, changing the toxic effects or beneficial effects of the drug. Ginkgo biloba, for example, has been demonstrated to reduce the area under the curve (AUC) for alprazolam & midazolam, two CYP3A4 enzyme substrates, suggesting possible inhibiting effects on drug metabolism. However, the pharmacokinetics of flurbiprofen and warfarin were unaffected by the identical plant, indicating that the effects of herbal remedies can differ depending on the medication and dosage [7,29]. The heterogeneity in herbal formulation hampers the estimation and assessment of HDIs, because many consumers self-medicate these medicines without consulting medical professionals, raising the probability of adverse reactions [29,30]. To clarify these HDIs and create guidelines for secure utilization of herbal remedies when combined with traditional medicines, systematic investigations are required [30,31].

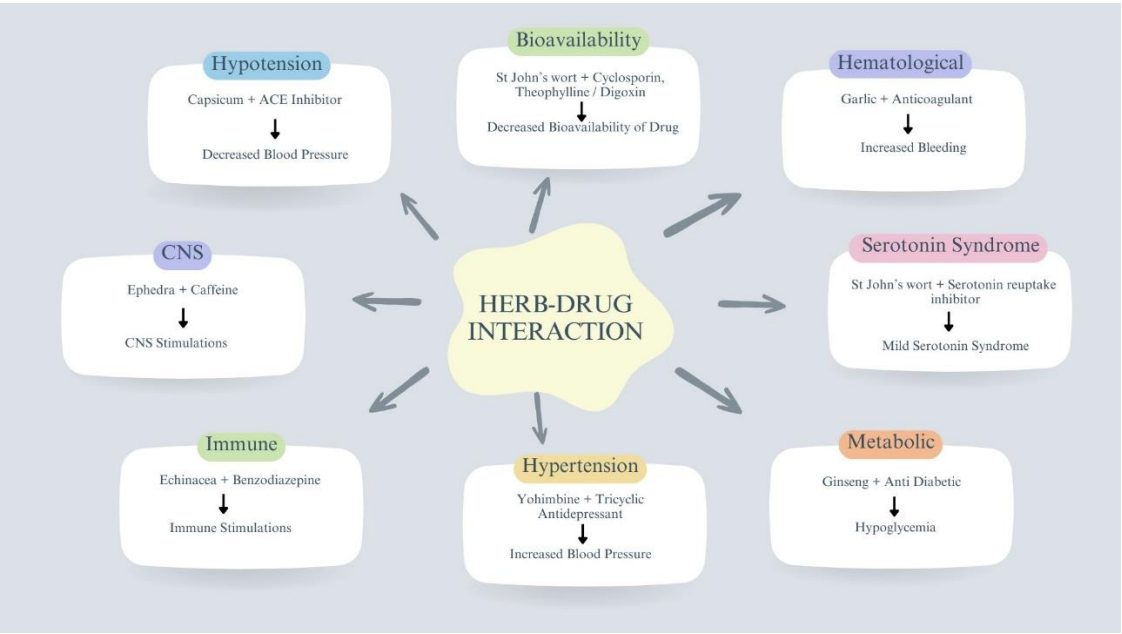

Figure 1. Common Herbs and Their Drug Interactions.

"Herbovigilance" is a surveillance and assurance of the responsible use of conventional drugs. Conventional medicines and their preparations are widely utilized to treat a wide range of ailments and health problems. But everyone believes that conventional treatments are risk-free and have zero adverse side effects. This misconception has been refuted by numerous scientific studies that show the frequency of adverse pharmacological reactions associated with herbal treatments. Pharmacovigilance, or the processes involved in the identification, evaluation, awareness, and avoidance of side effects or any other drug-associated difficulties, is crucial for the safety of herbal treatments. Although the already in use pharmacovigilance platforms were designed and executed successfully for synthetic pharmaceuticals, modifications are needed to take into consideration the distinct qualities and implications associated with natural goods [25,32].

4. Risk Factors

HDIs are a major problem in modern healthcare, especially as the utilization of herbal remedies grows alongside traditional therapies. The pharmacological qualities of both herbal remedies and traditional medicines, particular to the patient attributes, including the potency of the herbal formulations alone are some of the factors that increase the risk of adverse reactions (Table 1). A significant risk element is an individual's overall wellness. People who are experiencing comorbidity or individuals upon several drugs are more likely to acquire HDIs. Genetic variations can also affect the metabolism for both herbal and traditional drugs, compounding the effects of these interactions [33].

Herbal medications' pharmacokinetic and pharmacodynamic features are crucial when analysing HDIs. Most herbal items can inhibit the function of drug-metabolizing enzymes, specifically those in the cytochrome P450 family, resulting in changed drug concentrations in the body. For example, certain herbs can activate or block those enzymes, which results in either decreased efficacy or the increased toxicity of traditional medicines [3,29]. The potential for adverse interactions is increased when active ingredients in herbal remedies collaborate with protein carriers which help with drug absorption and excretion [29].

A further significant risk factor involves the "quality of herbal remedies." It is difficult to precisely evaluate the safety and efficacy of herbal remedies due to problems including adulteration, misidentification, and contamination, which can result in unforeseen pharmacological consequences. Unpredictable therapeutic effects & an elevated risk of interaction can also result from variations in the content of herbal products, which are frequently caused by variances in production and preparation techniques [3,33].

This scenario is complicated by the "lack of standardized guidelines" for assessing HDIs. There is still a lack of a systematic method for preventing and handling HDIs, despite the increasing awareness of the significance of keeping an eye on these interactions. Due to this lack of information, adverse reactions may go unreported and the dangers of using traditional and herbal remedies at the same time may be generally underestimated [29,33].

HDIs relate to a variety of risk parameters, including pharmacological features, product quality, patient preferences, and the requirement for standard assessment techniques. Since incorporating herbal remedies into contemporary medical regimens is becoming more and more popular, it is imperative that these factors be taken into consideration to ensure patient safety.

Table 1. Key Risk Factors for HDIs.

Risk Factor	Description
Patient Health Status	Comorbidities and polypharmacy increase the likelihood of adverse effects from HDIs [33].
Genetic Variability	Genetic differences impact drug metabolism, affecting the body's processing of both herbal and conventional drugs, and raising interaction risks [33].
Pharmacokinetic and Pharmacodynamic Properties	Many herbs influence drug-metabolizing enzymes (e.g., cytochrome P450), which can alter drug efficacy or increase toxicity [3,29].
Interaction with Protein Carriers	Active ingredients in herbs may interact with protein carriers, affecting drug absorption and excretion, and altering safety and effectiveness [29].
Quality of Herbal Products	Adulteration, contamination, and misidentification can lead to unforeseen effects, increasing the risk of adverse interactions [3,33].
Variability in Herbal Product Composition	Inconsistencies in the production and preparation of herbal products cause variations in content, leading to unpredictable therapeutic effects and interaction risks [3,33].
Lack of Standardized Guidelines	Limited systematic assessment methods for HDIs lead to underreported interactions and underestimated risks of combining herbal and traditional treatments [29,33].

5. Clinical Implications

HDIs are important clinical issues in contemporary medicine, especially given the increasing prevalence of simultaneous use of herbal remedies and prescription medications. Such interactions may cause patients' medications to become less effective, more toxic, or even have potentially fatal effects [4,34].

A major worry regarding HDIs is the diminished therapeutic effectiveness of traditional drugs. A variety of herbs can either stimulate or inhibit the cytochrome P450 group of enzymes, which is responsible for metabolizing drugs and changing the amounts throughout the human system [34,35]. Hypericum perforatum, the herb St. John's wort, is one example of a strong CYP3A4 trigger and can drastically decrease the plasma levels of medications processed by this enzyme, involving as immune-suppressive antiviral medications, and some chemotherapeutic medicines [3,34]. This combination may result in treatment failure for HIV-positive people, rejection of the organ in transplant patients, and decreased effectiveness of cancer treatments [3].

HDIs, on the other hand, can also raise the possibility of negative medication responses because of higher drug concentrations. Medicines including statins, Calcium channel blockers (CCBs), as well as benzodiazepines, are more widely distributed when taken in combination with herbs like grapefruit juice, which suppress gastrointestinal CYP3A4 [3,34]. An elevated risk of myopathy caused by statins, severe drowsiness from benzodiazepines, and potentially fatal arrhythmias from calcium channel blockers can arise from this combination [3].

The screening of HDIs risk is further complicated by the intricate and changeable composition of herbal preparations. It can be difficult to anticipate and control the interactions between various active ingredients found in many herbs, as they may interact with diverse pharmacological targets [29,35]. There is frequently a lack of regulation surrounding the safety and efficacy of herbal remedies, that raises the possibility of problems including adulteration, contamination, and inappropriate dosage [4,34].

Interactions between herbs and drugs present serious therapeutic difficulties for contemporary medicine. Elevated toxicity, decreased medication effectiveness, and possibly dangerous Adverse events (AEs) can result from such interactions. To guarantee patient safety and maximize therapeutic results, healthcare providers and patients need to be aware of the possible hazards connected with using herbal remedies and prescription medications together. They need to talk about and keep updated on such interactions.

6. Regulatory Considerations

Regulatory considerations over HDIs are increasingly significant in modern medical care because of the growing utilization of herbal remedies alongside standard drugs. The safety, efficacy, and quality of herbal medications are impacted by regulations, which vary widely across countries. For example, herbal products are governed under the Dietary Supplement Health and Education Act (DSHEA) in the USA, which classifies them as nutritious foods instead of drugs. The Food and Drug Administration (FDA) oversees it. It means that until and unless they are proven to present a significant risk, herbal remedies are treated for granted. It is the FDA's responsibilities to demonstrate this prior to a product gets withdrawn from distribution [4,29]. The shortage of recognized dosing and composition variation among herbal remedies further complicates the evaluation of their safety and the possibility of interactions. Whenever specific active ingredients in herbal remedies react with drug transporters and pharmaceutical-metabolizing enzymes, the pharmacokinetics and pharmacodynamics of combination pharmacological therapy get altered [34,36]. Healthcare providers might not possess enough access to accurate data about HDIs, that could cause patients' threats to go unidentified. For some, this inconsistency causes problems. Worldwide regulatory harmonization is required when disparities in regulatory standards may significantly impact the quality and reliability of products. The disparate ways that safety laws have been applied in different countries have left patients and medical personnel with a confusing patchwork of rules [36]. To enhance patient safety and optimize treatment outcomes, regulatory agencies should prioritize the evaluation of HDIs and provide explicit guidelines for the safe combination use of herbal medicines with conventional medications. This means promoting better communication about the application of herbal medicines between patients and medical professionals and ensuring that patients are informed of any potential risks associated with HDIs [29,34]. Regulatory frameworks are evolving to include guidelines for monitoring and managing HDIs, advocating for evidence-based approaches that ensure both safety and efficacy in the concurrent use of herbal and conventional medicines. Enhanced pharmacovigilance and research into the interactions between herbal products and pharmaceuticals are essential for safeguarding public health as the popularity of herbal remedies continues to rise [37,38].

HDIs are regulated differently by the Chinese Drug Evaluation (CDE), European Medicines Agency (EMA), as well as the Drug Management and Pharmaceutical Affairs (DMPA), each of these which reflects region-specific regulatory concerns. Herbal goods are subject to EU regulations through Guidelines 2001/83/EC & 2004/24/EC,

which mandate that conventional goods be registered simply or have full marketing approval. Herbs include St. John's Wort, that stimulates CYP450 enzymes and P-glycoprotein even may reduce plasma levels of medications including cyclosporine along with warfarin, are an emphasis of pharmacokinetic together with pharmacodynamic study used by the EMA to assess HDIs. Although HDI data is included in the monographs established through EMA's Committees upon Herbal Medicinal Products (HMPC), approximately 20% of them make inclusion of HDIs, suggesting most of the interaction require substantial clinical documentation [39,40]. The CDE in China requires comprehensive evaluations of HDIs throughout the drug manufacturing alongside regulatory process with the aim to guarantee the appropriate use of herbal remedies. It entails carrying out clinical studies and assessing pharmacological pathways. Regarding frequently utilized plants including ginseng and turmeric, DMPA guidelines mandate stringent pre-market assessments. Employing information from world-wide databases and regional instances, appliances include the Drug Interaction Probability Scale (DIPS) serve as vital for determining potential links among drugs and herbs [41]. Significant obstacles persist in the harmonization of worldwide HDI regulation requirements. Global commerce in herbal products is hampered by disparities in regulatory systems. In this regard, the U.S. FDA categorize herbal products as therapeutics or nutritional supplements depending upon their intended application, frequently avoiding the stringent pre-market reviews needed in Europe, while the EMA requires substantial proof for HDI labelling. immediate intervention is required to address this discrepancy to safeguard consumers and maintain a competitive advantage [40].

7. WHO Guidelines for HDIs

The World Health Organization (WHO) has issued recommendations for dealing with HDIs to improve the safety and efficacy of medical therapies that combine herbal treatments alongside conventional medications. These recommendations emphasize how important it is for medical practitioners to comprehend the pharmacokinetic and pharmacodynamic interactions that may occur when herbal medicines are taken with prescription drugs. Because herbal ingredients affect the enzymes and transporters that break down drugs, pharmacokinetic interactions can change how drugs are absorbed, distributed, metabolized, or excreted. On the other hand, pharmacodynamic interactions take place when herbs use comparable biological pathways to either increase or decrease the therapeutic effects of medications. WHO urges medical professionals to ask patients about all supplements they may be taking and stresses the value of informing patients about possible HDIs. To efficiently monitor side effects and interactions, the guidelines also support the incorporation of herbal remedies into current pharmacovigilance systems. WHO also urges greater research to better understand the mechanisms behind HDIs, which are still a poorly understood field of pharmacology. The ultimate objective is to improve patient outcomes in contemporary healthcare settings by giving medical practitioners all the materials they need to make educated decisions and guarantee secure simultaneous utilization of traditional and herbal medications [37,42].

8. Research and Future Directions

HDIs studies is becoming more vital in modern healthcare due to the increased usage of herbal supplements in conjunction with conventional pharmaceuticals. There is a high risk of negative interactions since users frequently self-administer these medications without telling their medical professionals. The body of current literature highlights the need for more thorough study, especially through observational studies that make use of real-world data, to comprehend the therapeutic implications of HDIs. Because of ethical considerations and the intricacy of herbal formulations, observational studies, for instance, might shed light on the prevalence and effects of HDIs in routine clinical settings, which are frequently missed in standard Randomized controlled trials (RCTs) [34,43]. Subsequent investigations ought to concentrate on formulating uniform approaches for evaluating HDIs, encompassing sophisticated computer models that forecast interactions predicated on the pharmacokinetic characteristics of the plant components. Furthermore, by utilizing cutting-edge study designs like case-control as well as cohort studies, we can improve our comprehension about these interactions and their practical consequences [43,44]. Increased interaction between scholars, medical practitioners, and government agencies is also necessary to develop thorough protocols that guarantee the secure incorporation of herbal items into treatment plans. In the end, this cooperative effort will enhance integrative medicine practices' therapeutic results and patient safety [4,29].

9. Conclusions

HDIs pose serious problems for contemporary medicine, requiring patients and healthcare professionals to exercise extra caution and awareness. The growing trend of using herbal supplements raises the possibility that they may negatively interact with prescription drugs, resulting in severe side effects or reduced therapeutic efficacy.

According to recent studies, these interactions involve both pharmacokinetic and pharmacodynamic pathways, with many herbs having the ability to modify drug metabolism and transport mechanisms. In clinical practice, there is often inadequate reporting and documenting, which contributes to the significant knowledge gap that persists despite the increasing body of information regarding interactions and their treatment consequences. Before prescribing medication, healthcare providers should have candid conversations with patients on the use of herbal supplements and the possibility of HDIs. Furthermore, more research is required to better our understanding of the mechanisms driving these interactions and to develop standard criteria. In the end, tackling the complexity of HDIs will help to improve integrative healthcare procedures and make them safer and more efficient. This will guarantee that patients can obtain the advantages of both conventional and herbal therapies without taking any risks.

Author Contributions: Conceptualization: P.K. Original draft preparation and writing: P.K., F.H., K.K. and A.G. Draft revision & editing: F.H., V.K. Final approval: P.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: Authors has declared there is no conflict of interest.

Ethical Approval: Not applicable.

Abbreviation

Abbreviation	**Full Form**
AEs	Adverse Events
AUC	Area Under the Curve
CCBs	Calcium Channel Blockers
CDE	Chinese Drug Evaluation
CYP450	Cytochrome P450
DIPS	Drug Interaction Probability Scale
DMPA	Drug Management and Pharmaceutical Affairs
DSHEA	Dietary Supplement Health and Education Act
EMA	European Medicines Agency
FDA	Food and Drug Administration
HDIs	Herb-Drug Interactions
HMPC	Committee on Herbal Medicinal Products
P-gp	P-Glycoprotein
RCTs	Randomized Controlled Trials
WHO	World Health Organization

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