International Research Journal of Education and Technology
Peer Reviewed Journal, ISSN 2581-7795
Impact Factor 5.007

Safety of Patients and Clinical Consequences of Herb-Drug Interactions and Toxicity

Dr. M. Gowthami[1], V. Niveditha Reddy[2], Madiha Faiyaz Ahmed [3], Asfia Anjum[4]

[1]Assistant Professor, Dept. of Pharmacy Practice, Malla Reddy College of Pharmacy
[2]Pharm D(PB) 1ST year & Malla Reddy College of Pharmacy,
[3]Pharm D(PB) 1ST year & Malla Reddy College of Pharmacy
[4]Pharm D(PB) 1ST year & Malla Reddy College of Pharmacy

Abstract

In the last several decades, the use of herbal medicines and complementary and alternative medicine (CAM) has grown a lot around the world. This has led to many people using them at the same time as traditional pharmacotherapy. People often think that herbal products are harmless since they come from nature. However, the bioactive compounds in these products can change the way drugs work in the body and how they affect the body, which can lead to clinically important herb-drug interactions. These interactions usually happen when cytochrome P450 enzymes, P-glycoprotein transporters, enzyme induction or inhibition, or pharmacodynamic processes that impact drug targets are changed. Some herbs that are often linked to this are Hypericum perforatum (St. John's wort), Ginkgo biloba, Allium sativum (garlic), Panax ginseng, and Zingiber officinale. These herbs may interact with anticoagulants, immunosuppressants, antidepressants, antiretrovirals, cardiovascular medications, and anticancer treatments. These kinds of interactions can cause toxicity, treatment failure, or bad clinical consequences such hepatotoxicity, nephrotoxicity, neurotoxicity, cardiovascular problems, and a higher risk of bleeding. Polypharmacy and changes in physiological conditions put vulnerable groups including the elderly, pregnant women, and people with chronic disorders at much greater danger. To keep patients safe, healthcare personnel need to do a full assessment of their drug history, talk to them about it, keep an eye on herbal use, and be involved in pharmacovigilance. Despite increasing clinical apprehension, obstacles such as insufficient clinical trials, regulatory discrepancies, underreporting, and inconsistency in herbal formulations endure. Future initiatives ought to emphasize evidence-based prescribing, enhanced regulatory frameworks, AI-driven interaction prediction, and customized medicine methodologies. In general, raising awareness and making it safer to use herbal medicines in clinical practice are both important for reducing risks and getting the best therapeutic results.

Key words: Herb-drug interactions; herbal remedies; toxicity; patient safety; cytochrome P450; pharmacokinetic interactions; pharmacodynamic interactions; complementary and alternative medicine; drug toxicity; pharmacovigilance.

1. Introduction:

Globally, the usage of herbal remedies, phytonutrients, and nutraceuticals is still growing quickly, with many individuals turning to these items in various national healthcare settings to treat a range of health issues [1] . Naturally, there has been a huge increase in public acceptance and interest in natural medicines over the past ten years in both developed and developing nations. These herbal cures are now sold not only in pharmacies but also in grocery shops and supermarkets. Up to four billion people, or 80% of the world's population, are thought to live in poor nations where herbal medicines are their main source of healthcare. Herbal medicine is also considered an essential part of traditional medicine [2].

It is uncertain that the expanding usage of complementary and alternative medicine (CAM) will slow down because it is a reflection of broader societal shifts and rising consumer demand for healthcare options. Even while CAM must adhere to the same safety and evidence standards as conventional medicine, many CAM therapies still lack scientific support, despite their growing popularity[3,4]. As a result, integrated medicine has emerged, combining some complementary and alternative medicine techniques with traditional therapies. In the end, ensuring safe and well-coordinated healthcare requires raising physician awareness and encouraging candid patient communication on CAM use [5,6]

Globally, more people are using herbal remedies in addition to traditional prescription medications, especially older persons and patients with chronic conditions. Unintentional interactions are more likely to occur since many people use herbal products in addition to prescription therapy without telling medical practitioners. Significant questions are raised by this expanding trend about therapeutic efficacy, treatment safety, and adverse event monitoring [7,8].

Drug pharmacokinetics or pharmacodynamics may be changed by herb–drug interactions, which could result in decreased therapeutic efficacy or increased toxicity. Drug transporters including P-glycoprotein and cytochrome P450 enzymes, which are essential for drug metabolism and distribution, are influenced by a variety of herbal ingredients. To improve rational medication and prevent unfavorable clinical consequences, systematic investigation of these interactions is crucial [9,10].

The goal of this paper is to give a thorough explanation of the underlying processes of clinically significant herb-drug interactions. It focuses on the clinical ramifications, toxicity hazards, and patient safety factors related to using conventional and herbal drugs at the same time. Strategies to raise knowledge and encourage a safer incorporation of herbal medications into clinical practice are also highlighted in the review [11].

2. Overview of Herbal Medicines:

Herbal medicines are preparations made from plants or plant parts that contain active phytochemical ingredients and are used for medicinal or preventative purposes. Based on processing and formulation, they are often divided into three categories: raw plant materials, herbal preparations (extracts, tinctures), and completed herbal medicinal products [12,13].

Commonly used herbal remedies for inflammatory, immunological, cardiovascular, and cognitive disorders include St. John's wort, ginkgo biloba, garlic, ginseng, ginger, turmeric, and echinacea. Cultural customs, ease of access, and the idea of natural safety are what make them so popular [13,14].

Different nations have different laws governing herbal remedies; some consider them to be nutritional supplements, while others treat them as pharmaceuticals. Requirements for quality, safety, efficacy evaluation, and post-marketing surveillance are impacted by variations in regulatory frameworks [15].

Because plant species, growth conditions, harvesting practices, and extraction techniques vary widely, it is difficult to standardize herbal medications. Clinical safety evaluation and quality assurance are complicated by problems such adulteration, contamination, and uneven phytochemical content [16].

3. Herb-Drug Interaction Concept:

When the bioactive ingredients in herbal remedies change the pharmacological action or disposition of prescription medications, this is known as a herb–drug interaction. Through pharmacokinetic or pharmacodynamic pathways, these interactions may alter the effectiveness of the medicine or enhance its toxicity. Understanding these interactions has become clinically significant due to the growing concurrent use of contemporary and traditional treatments [17,18].

Meaning

Changes in a drug's therapeutic response or toxicity brought on by co-administration of herbal medicines are known as herb-drug interactions.

Interference with medication metabolism, transport, or pharmacological activity causes these interactions. They could result in unfavourable clinical outcomes or treatment failure [18,19].

Interaction Types

Pharmacokinetic and pharmacodynamic interactions are the two main categories into which herb-drug interactions fall. While pharmacodynamic interactions modify the effects of drugs at the receptor or physiological level, pharmacokinetic interactions impact the absorption, distribution, metabolism, or excretion of drugs. Depending on the mechanism at play, both kinds could have positive or negative effects [20,21].

Clinical Significance

Particularly with medications with a limited therapeutic index, clinically significant herb-drug interactions may lead to decreased therapeutic efficacy, unanticipated side events, or toxicity. Herbal use has been connected in a number of studies to treatment failure and changed plasma medication concentrations. To reduce patient risk, healthcare workers must be aware [22].

Elements Affecting Interactions

The herbal composition, dose, length of usage, patient characteristics, and drug metabolic pathways all influence the likelihood of interactions. The severity of interactions is further influenced by genetic variability, polypharmacy, and variations in herbal preparation. Clinical risk is further increased by patient underreporting and a lack of uniformity [23].

3.1 Pharmacokinetic Interactions:

When herbal components change a medicine's absorption, metabolism, transport, or elimination, systemic drug concentrations are affected. This is known as pharmacokinetic herb–drug interactions. Modification of cytochrome P450 enzymes or drug transporters like P-glycoprotein is frequently involved in these interactions. Toxicity or treatment failure could result from altered bioavailability [24].

Absorption

Herbal preparations may alter drug absorption by affecting intestinal transporters, enzyme activity, or gastrointestinal pH. Oral medication bioavailability is impacted by certain herbs that change intestinal permeability or P-glycoprotein activity. Systemic drug exposure may rise or fall as a result of changes in absorption [24,25].

Distribution

Drugs may be dislodged from plasma protein binding sites by herbal components, changing the amount of free drug in the blood. Drug distribution in tissues can also be impacted by changes to transport proteins. These modifications could raise the risk of toxicity or improve pharmacological effects [26].

CYP450 Enzymes in Metabolism

The cytochrome P450 enzymes involved in drug metabolism are either induced or inhibited in many herb-drug interactions. While certain herbs inhibit CYP enzymes and raise the risk of toxicity, others, like St. John's wort, promote CYP3A4, which lowers plasma drug levels. A significant percentage of clinically significant interactions are caused by CYP modification.

Excretion

By affecting drug transporters or renal enzyme activity, herbal medications may change renal clearance. Urinary excretion changes can decrease the effectiveness of medication removal or lengthen its half-life. Adverse effects and drug buildup may be facilitated by this mechanism.

3.2 Interactions in Pharmacodynamics

When conventional and herbal medications act on identical physiological systems or receptors without changing drug concentration, this is known as pharmacodynamic interaction. Through antagonistic, synergistic, or additive effects, these interactions alter the therapeutic response. The combined pharmacological activities determine clinical outcomes [26.27].

Synergistic Impacts

When the effects of drugs and herbs complement one another and produce more pharmacological activity than either one alone, this is known as a synergistic interaction. For instance, when coupled with anticoagulants, herbs that have antiplatelet activity may make bleeding more likely. Depending on the clinical setting, these effects could be advantageous or detrimental [28,29].

Negative Impacts

When herbal products lessen or counteract pharmacological effect at the physiological or receptor levels, antagonistic interactions occur. This could result in treatment failure and reduce the effectiveness of medications. In the management of chronic diseases, these interactions are especially worrisome .

4. How herb-drug interactions work

Herb-drug interactions happen when phytochemicals change the way drugs work in the body by changing metabolic enzymes, transporters, or pharmacological targets. These processes may alter medication exposure, effectiveness, or toxicity, resulting in clinically important results [30,31].

Changing the activity of cytochrome P450 enzymes

Herbal components can influence cytochrome P450 (CYP) enzymes that facilitate medication metabolism, thereby modifying plasma drug concentrations. The induction or inhibition of CYP isoenzymes, including CYP3A4 and CYP2C9, constitutes a significant mechanism for herb-drug interactions [31,32].

Transporters for P-glycoprotein

P-glycoprotein (P-gp) is an efflux transporter that affects how drugs are absorbed and how they are removed from the body. Some herbal products change how it works. Modifications in P-glycoprotein activity can profoundly influence medication absorption and therapeutic efficacy [32,33].

Induction of enzymes

Some herbs boost the production or activity of metabolic enzymes, which speeds up medication metabolism and lowers drug levels in the body. This process might make medications less effective, especially those with limited therapeutic indices [33].

Enzyme Inhibition

Some herbal components stop enzymes that break down drugs, which makes drugs stay in the body longer and raises plasma drug levels. This kind of inhibition could cause drugs to build up in the body, which could lead to more side effects or toxicity [34].

Changing the Targets of Drugs

Herbal components may directly affect receptors or physiological processes that pharmaceuticals target, altering pharmacological effects without altering drug concentration. These pharmacodynamic interactions can yield synergistic, antagonistic, or additive effects [35].

5. Common Herbs That Can Interact With Drugs

Herbal medications possess pharmacologically active components that can alter drug metabolism, transport, or pharmacodynamic reactions. Numerous frequently utilized herbs are consistently linked to clinically relevant medication interactions shown in clinical and pharmacokinetic research [36,37].

5.1 St. John's Wort (Hypericum perforatum)

St. John's wort is a strong inducer of CYP3A4 and P-glycoprotein. This lowers the levels of medications including cyclosporine, warfarin, oral contraceptives, and antiretrovirals in the blood. This interaction could lead to treatment failure and rejection of the transplant [37,38].

5.2 Ginkgo (Ginkgo biloba)

Ginkgo has antiplatelet properties and may elevate the risk of bleeding when used in conjunction with anticoagulants or antithrombotic medications. It also affects CYP enzymes, which changes how drugs are broken down [39,40].

5.3 Garlic (Allium sativum)

Adding garlic to your diet can make antiplatelet effects stronger and may make bleeding worse when taken with warfarin or aspirin. It might also cause drug-metabolizing enzymes to work differently, which could impair several cardiovascular and antiviral medicines [40,41].

5.4 Ginseng (Panax ginseng)

Ginseng might change blood sugar levels and make anticoagulant medication, especially warfarin, less effective. There have also been reports of pharmacodynamic interactions between the central nervous system and the circulatory system [42].

5.5 Ginger (Zingiber officinale)

Ginger has effects on platelets and the movement of the stomach that could change how drugs are absorbed and raise the risk of bleeding when taken with blood thinners. The potential for interaction is primarily pharmacodynamic [43].

5.6 Other Herbs That Are Important for Health

Herbs including turmeric, echinacea, kava, and green tea have shown that they can interact with each other by changing the activity of CYP enzymes or adding to the toxicity of other substances. Variability in herbal composition leads to uncertain clinical consequences [44].

6. Drugs that herbal medicines often affect

Herbal items often interact with medications that possess narrow therapeutic indices or are processed by CYP450 enzymes and transport proteins. These interactions might change how much of a medicine is in the body and how well it works .

Warfarin and other anticoagulants

Herbs that have antiplatelet or CYP-modulating actions can make anticoagulants work better or worse, which might raise the risk of bleeding or thrombosis. Warfarin is one of the most commonly cited medications associated with herb–drug interactions .

Immunosuppressants (Cyclosporine, Tacrolimus)

St. John's wort significantly lowers immunosuppressant levels by inducing CYP3A4, which could lead to graft rejection in transplant recipients. Close monitoring of treatment drugs is very important [45].

Antidepressants

Herbal medicines that influence serotonin pathways may raise the risk of serotonin syndrome when taken with antidepressants. Pharmacodynamic interactions hold significant relevance in the context of serotonergic drugs [46].

Antiretrovirals

Herbal enzyme inducers lower the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors in the blood, which makes antiviral drugs less effective. There is a chance of treatment failure and resistance [47].

Drugs for the heart and blood vessels

Interactions with antihypertensives, digoxin, and antiarrhythmics may arise from modified metabolism or cumulative pharmacological effects. Changes in how well drugs work in the body can influence the stability of the heart and blood vessels .

Drugs that fight cancer

Herbal regulation of CYP enzymes and transporters can change the levels of chemotherapeutic drugs, which could make them less effective or more harmful. Patients with cancer are more at risk since they take many different drugs .

7. Toxicity Linked to Herb–Drug Interactions

Herb–drug interactions can result in organ toxicity or therapeutic problems due to modified drug exposure or cumulative pharmacological effects .

Hepatotoxicity

Some herbal items taken with hepatotoxic medicines may elevate liver enzymes and increase the risk of liver injury due to interactions between metabolic enzymes [48,49].

Nephrotoxicity

Herbal substances that influence renal clearance or have combined nephrotoxic effects can damage the kidneys and make it harder for drugs to leave the body [49,50].

Toxicity to the heart and blood vessels

Blood pressure, heart rate, or coagulation pathways can have additive effects that might cause arrhythmias or unstable hemodynamics [51].

Toxicity to the nervous system

Herbs that affect neurotransmitter systems may make CNS depression or overstimulation worse when taken with neuroactive medications [52].

Risk of Bleeding

When used with anticoagulants or NSAIDs, herbs that have antiplatelet activity greatly raise the risk of bleeding .

Failure of Treatment

Certain herbs can cause enzyme induction, which decreases medication levels and makes them less effective at treating diseases [53].

8. Clinical Implications

Herb–drug interactions can have a big effect on how well a treatment works by changing how much of a drug is in the body or how the body reacts to it. These interactions can make drugs less effective, cause unanticipated side effects, or make diseases worse, especially in people who are taking more than one medicine .

Effect on Treatment Results

Changes in how drugs are broken down or how they work in the body might lead to treatment failure or stronger effects of the drugs. Changes in the concentration of drugs in plasma can make treatment less effective and make it harder to predict how well a patient will do .

Risks in Particular Groups

Some categories of patients are more likely to have herb-drug interactions because of changes in their bodies, taking too many medications, and changes in how their bodies break down drugs. To avoid bad clinical effects, close monitoring is important .

Elderly

Older persons often use herbal supplements along with several prescription prescriptions, which can make drug interactions more likely because of changes in how the body processes pharmaceuticals as it gets older. Polypharmacy increases the risk of adverse medication responses even more .

Women Who Are Pregnant

Using herbs while pregnant could change how the mother metabolizes or how the fetus grows, and there isn't much safety data available. Possible interactions with prescribed drugs may endanger both the mother and the fetus .

People with Chronic Diseases

Patients with cardiovascular, diabetic, or oncologic illnesses frequently depend on long-term medication, rendering them especially susceptible to interaction-induced therapeutic failure or toxicity .

Adverse Drug Reactions and Hospitalization Clinically significant herb-drug interactions lead to avoidable severe medication responses and hospitalizations. Not telling doctors about herbal use makes diagnosis and treatment harder [54].

9. Things to think about for patient safety

To keep patients safe, doctors need to know about herbal medicine use and be ready to deal with possible interactions in the clinic. Adding herbal assessment to regular care helps lower the danger .

The significance of medication history

To find possible interactions, it is important to get a thorough medication history that includes the usage of herbal and nutritional supplements. Many patients do not willingly admit herbal usage .

Counseling for Patients

Teaching patients about the probable dangers of mixing herbal and traditional treatments helps them make better decisions and use medicines more safely .

Pharmacovigilance

Keeping an eye on and writing down bad occurrences that happen with herbal products can assist find interactions that weren't known about before. Pharmacovigilance systems are very important for making medicines safer .

What Healthcare Professionals Do

To reduce the hazards of using herbal medicines at the same time as other medicines, doctors and pharmacists should regularly check on how patients are using them, provide them evidence-based advice, and keep an eye on how well the treatments are working[55] .

Reporting Negative Reactions

Reporting suspected adverse events related to herbs improves safety databases and helps regulators make decisions. More reporting helps people comprehend the risks of interacting with others in the actual world .

10. Problems and gaps in knowledge

Even though many people take herbs, there are some problems that make it hard to accurately assess herb-drug interactions and their clinical importance .

No Clinical Trials

The majority of evidence about herb–drug interactions is derived from case reports or experimental investigations rather than extensive clinical trials. This makes it hard to draw clear conclusions on safety and effectiveness .

Bad Regulation

The rules for herbal medications are different in different parts of the world. In many cases, they don't have to go through as strict safety and effectiveness testing as regular drugs do .

Not reporting enough

Adverse effects associated with herbal products are often underreported due to insufficient awareness and the absence of standardized monitoring mechanisms.

Different Types of Herbal Preparations

Variations in plant species, growing conditions, and extraction methods result in uneven phytochemical compositions, complicating the prediction of interactions [56].

11.How to avoid and deal with problems

To effectively avoid and treat herb-drug interactions, clinicians need to keep a close eye on patients, make sure they are taking the right amount of herbs, and include herbal use in their regular assessments. Programs that teach healthcare workers and patients about the hazards and how to take medications safely can help people be more aware of them. Evidence-based prescribing and the incorporation of herbal medicine assessment into clinical decision-making mitigate unfavorable consequences and augment therapeutic efficacy [57].

12. What will happen in the future

Future strategies for minimizing herb–drug interactions must prioritize meticulously structured clinical research to produce dependable safety and efficacy data. Improvements in AI and computer modeling could help us better identify interaction hazards by looking at pharmacokinetic and molecular data. Enhancing regulatory frameworks and implementing personalized medicine approaches informed by genetic and metabolic diversity may further augment the safe utilization of herbal and conventional medicines [58].

13. Conclusion

Herb-drug interactions are a significant clinical issue because more and more people throughout the world are using both herbal treatments and pharmaceutical drugs at the same time. For early detection and prevention of bad outcomes, it is important to raise awareness among both healthcare professionals and patients. To safely add herbal medications to modern healthcare, we need to work together, use evidence-based evaluation, and keep up our efforts to watch for side effects [59].

REFERENCES:

1) WHO. (2004). *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*.Geneva, Switzerland: World Health Organization.
2) MukherjeeP. W. (2002). *Quality Control of Herbal Drugs: An Approach to Evaluation of Botanicals*.New Delhi, India: Business Horizons Publishers.
3) Chalmers I. Evidence of the effects of health care: a plea for a single standard across “orthodox” and “complementary” medicine. Complement Ther Med 1998; 6: 211-213.
4) Lewith G, Davies P. Complementary medicine: the need for audit. Complement Ther Med 1996; 4: 233-236.
5) Angell M, Kassirer JP. Alternative medicine — the risks of untested and unregulated remedies. N Engl J Med 1998; 339: 839-841.
6) Faass N. Integrating complementary medicine into health systems. Gaithersburg: Aspen Publications, 2001.
7) Fugh-Berman A. Herb–drug interactions. Lancet. 2000;355(9198):134-138.

8) Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777-1798.
9) Zhou S, Gao Y, Jiang W, Huang M, Xu A, Paxton JW. Interactions of herbs with cytochrome P450. Drug Metab Rev. 2003;35(1):35-98.
10) Wanwimolruk S, Prachayasittikul V. Cytochrome P450 enzyme mediated herbal drug interactions. EXCLI J. 2014;13:347-391.
11) Rombolà L, Scuteri D, Morrone LA, Bagetta G, et al. Pharmacokinetic interactions between herbal medicines and drugs. Life (Basel). 2020;10(7):106.
12) World Health Organization. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. Geneva: WHO; 2004.
13) Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777-1798.
14) Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.
15) Barnes J, Anderson LA, Phillipson JD. Herbal Medicines. 3rd ed. London: Pharmaceutical Press; 2007.
16) Kunle OF, Egharevba HO, Ahmadu PO. Standardization of herbal medicines — a review. Int J Biodivers Conserv. 2012;4(3):101-112.
17) Fasinu PS, Bouic PJ, Rosenkranz B. Herb–drug interactions: an overview of mechanisms and clinical evidence. Front Pharmacol. 2012;3:69.
18) Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs. Drugs. 2009;69(13):1777-1798.
19) Czigle S, Nagy M, Mladěnka P, et al. Pharmacokinetic and pharmacodynamic herb-drug interactions. PeerJ. 2023;11:e16149.
20) Choi S, Oh DS. Pharmacokinetic and pharmacodynamic interactions of herbal medicines. PLoS One. 2017;12:e0182794.
21) Rombolà L, Scuteri D, Morrone LA, et al. Pharmacokinetic interactions between herbal medicines and drugs. Life (Basel). 2020;10(7):106.
22) Babos MB, Mladěnka P, Filipský T. Herb–drug interactions: clinical perspectives. Toxicol Rep. 2021;8:1212-1221.
23) Choi YH, Chin YW, Kim YG. Herb–drug interactions and influencing factors. Pharmaceutics. 2020;12(7):610.
24) Cho HJ, Yoon IS. Pharmacokinetic herb–drug interactions via CYP and P-glycoprotein. Molecules. 2015;20(11):20288-20309.
25) Rengelshausen J, Göggelmann C, Burhenne J, et al. Pharmacokinetic herb–drug interactions. Clin Pharmacokinet. 2010;49(7):473-480.
26) Zhou S, Gao Y, Jiang W, et al. Interactions of herbs with cytochrome P450. Drug Metab Rev. 2003;35(1):35-98.
27) Wanwimolruk S, Prachayasittikul V. Cytochrome P450 mediated herbal drug interactions. EXCLI J. 2014;13:347-391.
28) Choi JG, Eom SM, Kim JH. Pharmacodynamic herb–drug interactions: mechanisms and evidence. J Ethnopharmacol. 2016;194:244-256.
29) Fasinu PS. Clinical significance of herb–drug interactions. Front Pharmacol. 2012;3:69.
30) Fasinu PS, Bouic PJ, Rosenkranz B. Herb–drug interactions: an overview of mechanisms and clinical evidence. Front Pharmacol. 2012;3:69.

31) Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777-1798.
32) Zhou S, Gao Y, Jiang W, Huang M, Xu A, Paxton JW. Interactions of herbs with cytochrome P450. Drug Metab Rev. 2003;35(1):35-98.
33) Cho HJ, Yoon IS. Pharmacokinetic herb–drug interactions involving transporters. Molecules. 2015;20(11):20288-20309.
34) Wanwimolruk S, Prachayasittikul V. Cytochrome P450 mediated herbal drug interactions. EXCLI J. 2014;13:347-391.
35) Choi JG, Eom SM, Kim JH. Pharmacodynamic herb–drug interactions: mechanisms and clinical relevance. J Ethnopharmacol. 2016;194:244-256.
36) Fasinu PS, Bouic PJ, Rosenkranz B. Herb–drug interactions: overview of mechanisms and clinical evidence. Front Pharmacol. 2012;3:69.
37) Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs. Drugs. 2009;69(13):1777-1798.
38) Nicolussi S, Drewe J, Butterweck V, Meyer zu Schwabedissen HE. Clinical relevance of St John's wort drug interactions. Br J Pharmacol. 2020;177(6):1212-1226.
39) Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with Ginkgo biloba. J Gen Intern Med. 2005;20(7):657-661.
40) Ekor M. The growing use of herbal medicines and safety concerns. Front Pharmacol. 2014;4:177.
41) Ulbricht C, Basch E, Szapary P, et al. Garlic interactions and safety review. J Herb Pharmacother. 2004;4(1):1-20.
42) Yuan CS, Wei G, Dey L, et al. Interaction between ginseng and warfarin. Ann Intern Med. 2004;141(1):23-27.
43) Marx W, McCarthy AL, Ried K, et al. Ginger mechanisms and clinical effects. Nutrients. 2015;7(8):6453-6469.
44) Posadzki P, Watson LK, Ernst E. Herb–drug interactions: systematic review. Br J Clin Pharmacol. 2013;75(3):603-618.
45) Rengelshausen J, Göggelmann C, Burhenne J, et al. Pharmacokinetic herb interactions. Clin Pharmacokinet. 2010;49(7):473-480.
46) Fugh-Berman A. Herb–drug interactions. Lancet. 2000;355(9198):134-138.
47) Piscitelli SC, Burstein AH, Welden N, et al. St John's wort and indinavir interaction. Lancet. 2000;355(9203):547-548.
48) Meijerman I, Beijnen JH, Schellens JH. Herb–drug interactions in oncology. Oncologist. 2006;11(7):742-752.
49) Teschke R, Schulze J. Herbal hepatotoxicity mechanisms. J Clin Transl Hepatol. 2016;4(2):80-89.
50) Yang B, Xie Y, Guo M. Herbal toxicity and organ damage. Front Pharmacol. 2018;9:1481.
51) Perazella MA. Herbal nephrotoxicity review. Clin J Am Soc Nephrol. 2010;5(6):1139-1149.
52) Gurley BJ, Swain A, Hubbard MA, et al. Clinical assessment of herb interactions. Clin Pharmacol Ther. 2008;83(1):61-69.
53) Spinella M. Herbal medicines and CNS interactions. Am J Health Syst Pharm. 2001;58(11):1080-1086.
54) Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777-1798.

55) Agbabiaka TB, Wider B, Watson LK, Goodman C. Concurrent use of prescription drugs and herbal medicinal products in older adults: a systematic review. Drugs Aging**.** 2017;34(12):891-905.
56) Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.
57) Fasinu PS, Bouic PJ, Rosenkranz B. Herb–drug interactions: an overview of mechanisms and clinical evidence. Front Pharmacol**.** 2012;3:69.
58) Rombolà L, Scuteri D, Morrone LA, Bagetta G, et al. Pharmacokinetic interactions between herbal medicines and drugs: mechanisms and clinical relevance. Life (Basel**).** 2020;10(7):106.
59) Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.