Drugs - Real World Outcomes (2023) 10:577–585
https://doi.org/10.1007/s40801-023-00388-w

ORIGINAL RESEARCH ARTICLE

Signal Detection and Assessment of Herb–Drug Interactions: Saudi Food and Drug Authority Experience

Waad Alghamdi[1] · Nouf Al-Fadel[1] · Eman A. Alghamdi[1] · Maha Alghamdi[1] · Fawaz Alharbi[1]

Accepted: 14 August 2023 / Published online: 19 October 2023

Abstract

Introduction Numerous investigations on herbal medicine that have been undertaken in the past several years demonstrate the general acceptance of its safety. The Saudi Food and Drug Authority (SFDA) established the Herb–Drug Interaction (HDI) project to detect and assess potential HDIs to ensure safety. The aim is to detect safety signals and assess them based on available evidence.

Methods First, SFDA-registered herbal products ($n = 30$) were selected and prioritized based on commonly used herbs. Second, reported potential HDIs were retrieved from the World Health Organization global database of individual case safety reports (VigiBase), AdisInsight®, and the Natural Medicines database. We excluded drugs non-registered by SFDA and labeled interactions in the product information of SFDA, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA). Finally, a comprehensive evaluation of potential HDIs was carried out using several evidence sources: literature, global cases, local cases, and other relevant documents. The Drug Interaction Probability Scale (DIPS) scale was used to assess the probability of a causal relationship between the interacting herb and drug and the event.

Results The search yielded 566 potential signals, and 41 had published evidence and were referred for assessment. The assessment results using DIPS were: 22 possible (53.6 %), 7 probable (17%), and 12 doubtful (29.2%) interactions. The recommendation was to include probable HDIs in the product information, including turmeric–tacrolimus, etoposide–*Echinacea*, *Ginkgo biloba*–ibuprofen, green tea–warfarin, and licorice–thiazides interactions.

Conclusion The HDI project assessed the screening and identification of potential HDIs. The action plan of this project can be used in post-marketing activities to identify potential drug interactions.

Key Points

The analysis of potential HDIs is more complex than potential drug–drug interactions, given that herbal products contain multiple active ingredients compared with drugs.

This study exemplifies a unique pharmacovigilance practice focusing on herbal product safety, demonstrating how to systematically identify and assess case reports of potential HDIs.

The application of the Drug Interaction Probability Scale (DIPS) is validated as an effective tool in the context of pharmacovigilance, providing valuable insights into the likelihood of reported potential HDIs.

✉ Waad Alghamdi
waad.m.alghamdi@gmail.com

Nouf Al-Fadel
nsfadel@sfda.gov.sa

Eman A. Alghamdi
Eaghamdi@sfda.gov.sa

Maha Alghamdi
mh.ghamdi@sfda.gov.sa

Fawaz Alharbi
Ffharbi@sfda.gov.sa

[1] Saudi Food and Drug Authority, Riyadh, Saudi Arabia

1 Introduction

Herbal medicinal products (HMPs) are a subset of complementary and alternative medicine that encompasses a wide range of procedures and items that have evolved [1]. According to recent research in Saudi Arabia involving 1300 people, around 1226 subjects (94%) of the included cohort utilized herbal medications for therapeutic purposes [2]. The study revealed a high level of usage of herbal medicines in Saudi Arabia, primarily owing to traditional beliefs and family influence [2]. In Saudi Arabia, some people think that herbal therapy is safer, more efficient, and more affordable than conventional medications [2]. The use of herbal remedies that have not been scientifically evaluated is common, and their risks are not fully understood [2] despite the fact that they are used extensively [3]. Although the safety profile of HMPs is encouraging [3, 4], cumulative data indicate major drug interactions, which can put patients at great risk [5–9].

The likelihood of herb–drug interactions (HDIs) might be higher than that of drug–drug interactions (DDIs) because HMPs usually contain combinations of pharmacologically active ingredients, as opposed to pharmaceuticals, which often contain single chemical entities [5]. Drug interaction is a clinical phenomenon that can occur when the therapeutic effect is either increased, decreased, or transformed into a toxic effect owing to the co-administration of another substance, which can result in treatment failure, a life-threatening side effect, or a minor side effect [6]. The World Health Organization (WHO) reported that approximately 80% of people globally use traditional, mainly herbal, medicines for their primary healthcare. Despite their popularity, these medicines face issues such as the sustainability of plant resources, variable quality, and difficulties in conducting clinical trials owing to challenges in creating identical placebo controls. Existing regulations also have loopholes that may affect the safety and efficacy of herbal drugs. To address these issues, updated methodologies, better regulatory guidelines, and integration of traditional medicine into national healthcare systems are recommended [7].

The number of published reported cases of potential HDIs is relatively low; this may be due to the potential low reporting of such cases by healthcare professionals and patients given that some patients might use herbal supplements without seeking medical advice, and the lack of clear plausible mechanisms for such interactions. However, researchers have looked into this with a broad focus as one study reviewed potential HDIs using real-world evidence [8]. Herbal medicine's global popularity increases the chance of its concurrent use with conventional drugs that may lead to adverse events due to potential HDI [9]. However, only a few studies have explored these interactions' real-world clinical consequences. Given that clinical trials may take a long time to conduct, observational studies are usually considered as an alternative for investigating potential HDI [10]. Monitoring of adverse reactions from potential HDI in pharmacovigilance activities of regulatory bodies and marketing authorization holders is very important to identify and assess and manage the risks because of the lack of regulated of herbal products and the wide use of these products worldwide. Awareness among healthcare professionals, consumers, and suppliers is vital through national pharmacovigilance centers that play a key role to promote adverse event reporting [11–13].

Herbal products have been implemented into pharmacovigilance systems in several regulatory agencies worldwide to identify potential risks related to herbs. The United States (US) Food and Drug Administration (FDA) released safety alerts for the public about the use of herbal medicines [7, 10, 11, 14–16]. Healthcare professionals are reminded to ask patients about the use of natural health products when prescribing and dispensing conventional medications. The European Medicines Agency (EMA) released guidelines on the investigation of drug interactions, including herbal supplements [12]. In addition, herbal companies are obligated to conduct pharmacovigilance for their products and notify the regulatory authorities of any suspected adverse events [13, 17].

In 2021, the Saudi Food and Drug Authority (SFDA) initiated the HDI project. This project aims to detect potential safety signals related to HDIs and assess the signals based on scientific evidence to ensure the safe use of conventional medicines and herbal products. Ultimately, the project outcomes will ensure medication safety in Saudi Arabia by providing up-to-date information for healthcare professionals and patients and by raising awareness about potential HDI among healthcare providers and patients [18].

2 Methods

2.1 Research Methodology

In the initial stage of the study, we selected SFDA-registered herbal products on the basis of quantitative data regarding their local and global usage. For each selected herbal product, we conducted a thorough search for reported potential HDIs across several databases: the World Health Organization (WHO) global Individual Case Safety Report (VigiBase) [19], the national pharmacovigilance center at SFDA, AdisInsight [20], and the Natural Medicines Database [21].

Secondly, we checked the labeling of retrieved potential HDI cases in the local product information. If the interaction is not labeled, we screened the product information (PI)

of the international regulatory agencies namely the United States Food and Drug Administration (US-FDA), the European Medicines Agency (EMA), and Health Canada product information to exclude any labeled interactions. A request for product safety information update was performed for interactions not labeled in the local PI but labeled in other international stringent regulatory agencies. When we refer to "local product information," we are specifically referring to the detailed information provided with the product, often referred to as the product information (PI) or summary of product characteristics (SPC) or drug label, that includes information about the product's contents, usage instructions, potential side effects, and interactions.

Lastly, each potential signal (with more than two sources of evidence) was then rigorously evaluated by a comprehensive safety reviews. This evaluation process was based on evidence gathered from various sources including scientific literature, local cases and global cases, and review documents from stringent regulatory authorities. We defined our search strategy with specific keywords related to each selected herbal product and potential drug interactions. Databases such as PubMed, Cochrane, and Google Scholar were used for the literature search. Full-text articles were then assessed, and data were extracted systematically. The Drug Interaction Probability Scale (DIPS) was used to objectively assess the likelihood of a causal relationship between the potential drug interactions and the observed adverse events. The scale assesses factors such as the quality of the evidence for the interaction (e.g., positive de-challenge/re-challenge), the biological plausibility of the interaction, and the presence of other risk factors that could increase the incidence of the adverse reaction. All these details and actions taken at every step were aimed at providing the highest level of scientific rigor and integrity to our study.

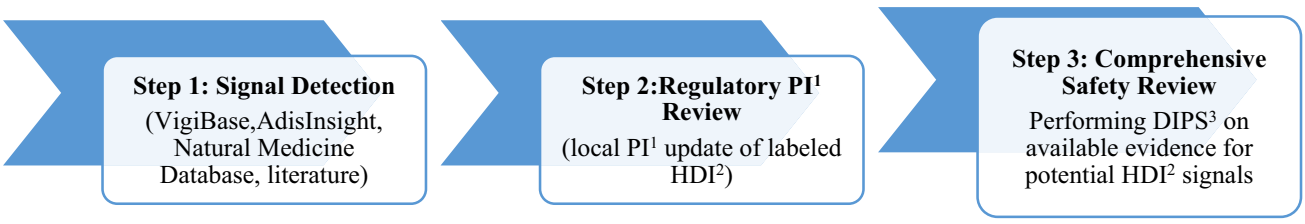
On the basis of the available evidence included in the comprehensive safety review, a regulatory action may be recommended, such as updating the product safety information (PI). The research period was performed from January 2021 to October 2022. The steps of the assessment are further explained in Fig. 1.

3 Results

A total of 30 herbal products were selected with 566 potential HDI signals. Of the 566 potential interactions, 161 potential interactions were detected from more than one database.

Performing a search in VigiBase [19] using the keyword "Herbal interaction" as a preferred term (PT) yielded a total of 146 potential HDIs. Most of the reported potential HDIs were in the age group of 18–44 years (16%) old. The top reported interacting active ingredients were *Ginkgo biloba*, quetiapine, ginseng, warfarin, and paroxetine, respectively (Figure 2). It is important to clarify that concomitant medications refer to the drugs and supplements that participants are taking alongside the prescribed medications and treatments involved in treatment regimen. These concomitant medications are additional and may have an impact on the overall outcomes [8]. The most reported reactions of potential HDIs were drug interactions, dizziness, drug-induced liver disease, serotonin syndrome, headache, and gastrointestinal hemorrhage, respectively (Fig. 3). A total of 86 cases were serious (58.9%). According to seriousness criteria, most serious cases led to medically important conditions (52.1%), prolonged hospitalization (18.5%), the threat to life (4.8%), and death (3.4%).

The assessment of potential HDI on the basis of comparing the local product information with stringent regulatory authority product information resulted in a local label update for 11 products (6 herbal and 5 medicinal products) (Table 1). Of the 161 potential interactions detected, 41 signals for ten herbal products had published evidence and a set for further evaluation (Fig. 4). Ten comprehensive drug safety reviews were performed to assess 41 potential interactions for 10 herbal products. The herbal products were turmeric, *Echinacea*, flaxseed, *Ginkgo biloba*, ginseng, green tea, hibiscus, licorice, milk thistle, and *Rhodiola*. According to the DIPS tool and on the basis of the available evidence, the results of potential HDIs assessment were 22 possibly related (53.6 %), 7 probably related (17%), and 12 doubtful relations (29.2%) (Table 2).



(1) PI: Product Information, (2) HDI: Herb-Drug Interaction, (3) DIPS: Drug Interaction Probability Scale.

Fig. 1 Steps of HDI signal detection and assessment

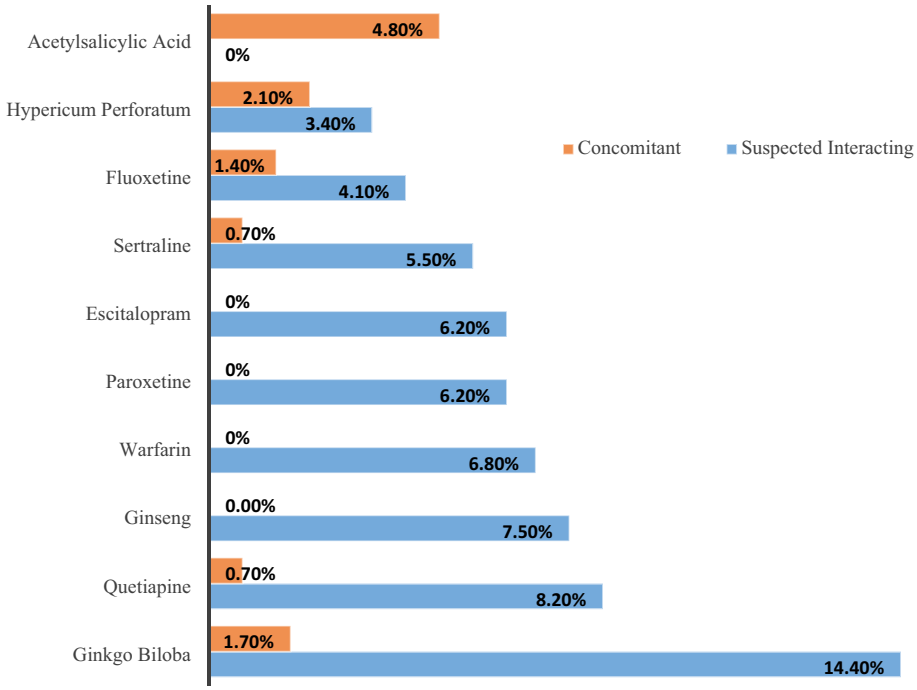


Fig. 2 Top reported interacting herb. AI: active ingredient. Suspected interacting: if an adverse drug reaction is suspected of being related to a drug interaction between two or more drugs. Concomitant: drugs used concurrently but not suspected by the reporter to have caused the adverse event of the interaction

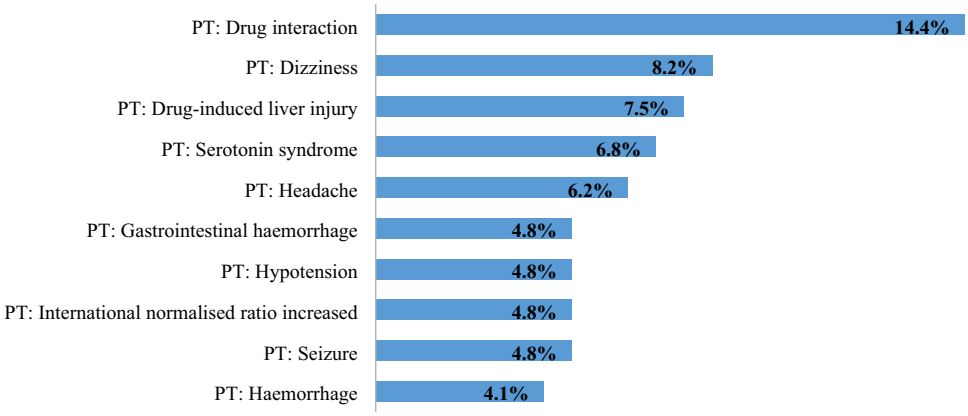


Fig. 3 Top co-reported reactions as a preferred term (PT). PT: preferred term

Our study primarily focuses on herbal medicines and their interactions with other drugs. To align with this focus, we have gathered local product information (PI) updates specific to herbal ingredients. Table 1 highlights some key interactions identified.

4 Discussion

Pharmacovigilance is the science and activity related to the detection, assessment, understanding, and prevention of adverse effects or any problems related to medicinal products [22]. Many patients use herbs/herbal supplements as an alternative and/or adjunct to their prescribed medicine. Herbal products are used by 20% of the population in the USA [23]. There are many risks with the use of herbal products (Fig. 5) [23].

By exploring various elements related to the interaction between herbal products and drugs, this study aim to shed light on the complexities involved and provide comprehensive insights.

Interactions with conventional medications: Herbal products have the potential to interact with commonly prescribed medications. These interactions can affect the efficacy and safety profiles of both the herbal products and the drugs involved. It is important to assess these interactions thoroughly to prevent adverse effects or reduced therapeutic outcomes.

Pharmacokinetic interactions: Herbal products may influence the absorption, distribution, metabolism, and excretion of drugs through pharmacokinetic interactions. These

Table 1 Regulatory product information (PI) update

Active ingredient	Local PI update
Turmeric	Interaction with clopidogrel
Echinacea	Interaction with drugs metabolized by cytochrome P450 1A2
Ginseng	Interaction with warfarin
	Interaction with digoxin
Senna	Interaction with digoxin
Fenugreek	Interaction with darfarin
Aspirin	Interaction with turmeric
Clopidogrel	Interaction with turmeric
Digoxin	Interaction with senna
	Interaction with ginseng
Fluoxetine	Interaction with *Ginkgo biloba*
Warfarin	Interaction with fenugreek

PI: product information

interactions can alter drug levels in the body, leading to potential therapeutic failures or toxicity. Understanding the mechanisms behind these interactions is crucial for optimizing treatment regimens and minimizing risks.

Pharmacodynamic interactions: Herbal products may also exhibit pharmacodynamic interactions, affecting the physiological and biochemical mechanisms of drugs. These interactions can alter drug responses, exacerbate side effects, or produce unpredictable outcomes. Identifying and characterizing these interactions can guide clinicians and patients in making informed decisions regarding the combined use of herbal products and conventional medications.

Variability in product composition: Herbal products often contain multiple active compounds, which can vary in concentration and quality between different products and brands. This variability poses challenges in accurately assessing their safety and efficacy profiles. Standardization and quality control measures are essential to ensure consistent product composition and reduce the potential risks associated with variations in herbal product formulations. Other than the effects of the biologically active constituents of the plant, side effects may happen owing to the potential HDI or contaminants [23].

Van Hunsel et al. [24] performed an analysis of the adverse events reports related to HMPs and herbal supplements in the Dutch pharmacovigilance database. Lareb received 789 submissions associated with herbal medicinal products and herbal supplements. These submissions implicated 823 distinct herbal products as potentially problematic, resulting in 1727 instances of adverse drug reactions. Among the 823 implicated products, 229 were officially registered as medicines, while the remaining 594 were marketed as herbal supplements. Reports related to single-herb products accounted for 522 cases, with the remaining 256 reports were about multi-herb combinations. Among all these, there were 22 documented instances of potential HDIs [24].

In our research, we pinpointed 41 possible drug interactions across 10 herbal products. To evaluate the connection between these potential interactions and potential HDIs, we employed the Drug Interaction Probability Scale (DIPS). This process requires meticulous examination of not only the characteristics of the drugs involved but also individual patient factors and potential influences of other concurrent medications. The purpose of this scale is to aid in the identification of adverse outcomes that could be attributed to drug interactions. The DIPS guides this evaluation through a sequence of questions specific to the suspected drug interaction, facilitating the estimation of a probability score. To perform an accurate assessment using DIPS, a comprehensive understanding of the pharmacological aspects of both the drug being acted upon (the object) and the drug causing the action (the precipitant) is necessary (Appendix 1) [25].

According to the DIPS, we found a probable association between turmeric and tacrolimus interaction. Turmeric

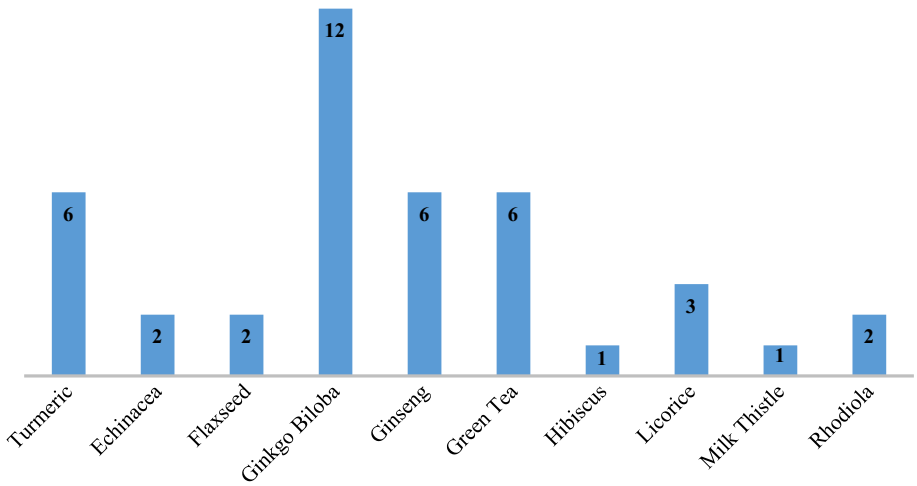


Fig. 4 Number of interacting drugs per herb

Table 2 Potential interactions assessment using Drug Interaction Probability Scale (DIPS)

Herbal ingredient	Potential interaction signal	Probability scale*
Turmeric	Warfarin	Possible
	Clopidogrel	Possible
	Aspirin	Possible
	Loratadine	Doubtful
	Tacrolimus	Probable
	Paclitaxel	Doubtful
Echinacea	Etoposide	Probable
	Darunavir	Possible
Flaxseed	Warfarin	Possible
	Clopidogrel	Possible
Ginkgo biloba	Ibuprofen	Probable
	Acetaminophen	Doubtful
	Aspirin	Possible
	Escitalopram	Possible
	Sertraline	Possible
	Fluoxetine	Possible
	Paroxetine	Possible
	Zolpidem	Possible
	Diazepam	Possible
	Alprazolam	Possible
	Risperidone	Possible
	Clopidogrel	Possible
Green tea	Warfarin	Probable
	Simvastatin,	Possible
	Atorvastatin	Doubtful
	Rosuvastatin	Doubtful
	Lisinopril	Doubtful
	Ramipril	Doubtful
Licorice	Indapamide	Probable
	Chlorthalidone	Probable
	Hydrochlorothiazide	Probable
Ginseng	Clopidogrel	Doubtful
	Aspirin	Doubtful
	Apixaban	Doubtful
	Paroxetine	Possible
	Lamotrigine	Possible
	Phenelzine	Doubtful
Hibiscus	Erlotinib	Possible
Milk thistle	Ritonavir	Possible
Rhodiola	Escitalopram	Doubtful
	Paroxetine	Possible

*Assessment using Drug Interaction Probability Scale (DIPS) (Appendix 1)

increases the level of tacrolimus owing to cytochrome P450-3A4 (CYP3A4) inhibition [26, 27]. Several cases reporting this interaction have been published [28–30]. People taking tacrolimus are advised to avoid large doses

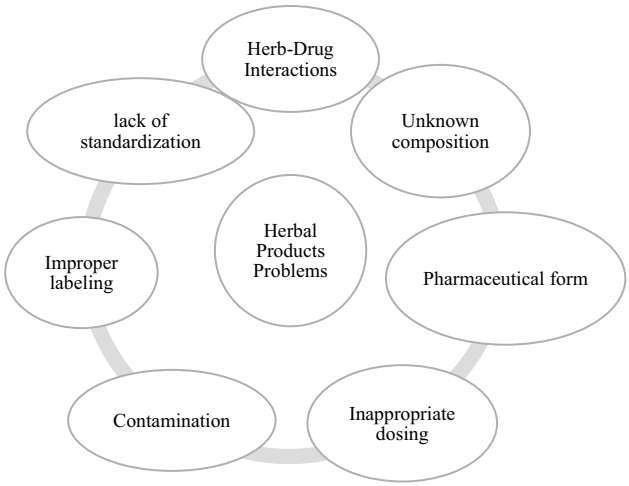


Fig. 5 Potential risks with herbal products [23]

of turmeric. A potential interaction between *Echinacea* and etoposide was also probable. Etoposide is a potential substrate of the p-glycoprotein transporter system. Thus, a potential interaction mechanism is *Echinacea* inhibition of the P-glycoprotein transporter system leading to an increase in substrate concentration, such as etoposide [31]. *Echinacea* could also inhibit intestinal CYP 3A4 and induce hepatic CYP 3A4, which mediates the metabolism of etoposide. There has been one published case discussing the interaction between *Echinacea* and etoposide [32]. It was found that the patient had been self-treating with *Echinacea* and experienced thrombocytopenia. The authors of the case report suggested that the *Echinacea* inhibited the CYP3A-mediated metabolism of etoposide, leading to an increase in etoposide levels and effects. Caution has been advised regarding the concomitant intake of *Echinacea* and etoposide; furthermore, one should discontinue *Echinacea* intake before chemotherapy [33].

Flaxseed contains omega-3 fatty acids such as linolenic acid, which is thought to have some antiplatelet effects and might therefore prolong bleeding time. Theoretically, this effect might be additive to that of other antiplatelet drugs and increase the risk of bleeding with anticoagulants [34]. Other reviews also stated that the interaction mechanism decreased platelet aggregation and increased bleeding time, which could lead to an increased risk of bleeding or bruising [34]. Using the DIPS, we found probable interaction with clopidogrel [35] and possible interaction with warfarin [36]. A positive re-challenge was found between flaxseed oil and bruising intensity while taking clopidogrel [35]. We also found a potential interaction between *Ginkgo biloba* and nonsteroidal anti-inflammatory drugs (NSAIDs). The assessment of interaction according to DIPS was probable. The available evidence suggests a potential pharmacodynamics interaction between NSAIDs and *Ginkgo biloba*. The

interaction between *Ginkgo biloba* and NSAIDs is plausibly related to their conferred anticoagulant effects. Aspirin and NSAIDs are believed to produce a systemic bleeding tendency by impairing thromboxane-dependent platelet aggregation and consequently prolonging the bleeding time [37]. *Ginkgo biloba* has a biologically plausible mechanism for increased risk of bleeding through interactions with platelet-activating factor (PAF) and collagen that lead to decreased platelet aggregation [19, 20]. The studies suggested that *Ginkgo biloba* might potentiate the effects of drugs with anticoagulant or antiplatelet effects. There are several published cases addressing potential interactions between *Ginkgo biloba* and NSAIDs [38–45].

We also found a probable interaction according to DIPS between green tea and warfarin. Animal and in vitro data suggest that green tea constituents may have antiplatelet properties [46, 47]. Moreover, epidemiologic studies have found evidence of an inverse association between green tea consumption and the risk of stroke [48]. Published evidence of the potential interaction also exists [49]. We observed a probable relationship between licorice and thiazide diuretics interaction as well. Licorice extract has mineralocorticoid-like effects and can cause hypokalemia, hypertension, cardiac arrhythmia, and myopathy.

Pharmacodynamic interactions are possible with concomitant use of licorice and potassium-depleting diuretics (e.g., thiazides or loop diuretics) by increasing the risk of developing hypokalemia [50]. A randomized trial showed that combining even a low dose of licorice with hydrochlorothiazide treatment would lead to a high risk of hypokalemia in healthy people. It is crucial for patients taking these medicines to avoid regular consumption of licorice [51]. There are also five published cases discussing the same interaction [52–56].

With the growing use of herbal medicines globally, safety is therefore important. Usually, herbal remedies are combined with other medications. Thus, it is important to understand the results of such a combination and whether regulatory authorities may issue ADRs, which can follow the existing pharmacovigilance system. For this purpose, the WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems was established in 2004. The guideline describes the safety monitoring of herbal medicines including sources of reports, herbal products targeted for safety monitoring, reporting of suspected ADRs, assessment of case reports and data management, and risk communication. Although the assessment of case reports was described using WHO causality categories, the risk assessment for potential HDI was not discussed [57].

There are challenges facing herbal pharmacovigilance, which include harmonization of herb naming systems (herbal drug name, pharmaceutical name, botanical or common name), which are not faced by synthetic medicines [58]. The lack of potential HDI reporting is also an issue. At the international scale, the WHO-UMC already compiles a small number of adverse potential HDI reports from national pharmacovigilance centers. While individual reporting countries retain ownership of and publishing rights to their data, aggregating the adverse potential HDI data from all member countries would be valuable for ongoing research. All countries' national reporting systems should record potential HDI reactions, which will then be reported to the WHO [11].

Currently, there are no published papers addressing the regulatory practices of assessment of potential HDI. There is a need to include potential HDI detection and assessment practice from a regulatory perspective. Our study provides a potential pharmacovigilance method to identify and assess reported potential HDIs.

4.1 Limitations of the Study

Our study's limitations do not quantify the strength of the association of potential HDI owing to the voluntary nature of case reporting and lack of exposure data. The study also relied on preexisting databases, which may not cover all possible herbal products and drug interactions globally. Furthermore, the Drug Interaction Probability Scale (DIPS) used is subjective and dependent on the researcher's interpretation. There could be variations in the product compositions, as herbal products are not as stringently regulated as pharmaceuticals.

5 Conclusions

The HDI project consists in assessment by the SFDA for identification of new safety signals related to potential HDIs. The process of this project can be used in post-marketing activities to identify any potential drug interactions. The results of this project emphasize the necessity of implementing "Pharmacovigilance of Herbal Products" in our national system. The detection of potential herbal drug interaction can be addressed by improving awareness to report suspected HDI, performing pharmacoepidemiologic studies, reviewing the current evidence, asking experts for counseling, and ensuring that herbal companies implement a pharmacovigilance system for their products. Healthcare professionals are also advised to include potential HDIs as part of their patient counseling routine.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-023-00388-w.

Declarations

Funding The study did not receive financial support.

Conflict of Interest W.A., E.A., M.A., N.A. and F.A. declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions Data collection was performed by W.A., E.A., and M.A. Data analysis was performed by W.A. The first draft of the manuscript was written by W.A., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Wachtel-Galor S, Benzie IFF. Herbal medicine. In: Herbal medicine: biomolecular and clinical aspects. 2nd ed. CRC Press/Taylor & Francis; 2011. p. 1–10.
2. Alkhamaiseh SI, Aljofan M. Prevalence of use and reported side effects of herbal medicine among adults in Saudi Arabia. Complement Ther Med. 2020;48:102255.
3. Al-Faris EA, Al-Rowais N, Mohamed AG, Al-Rukban MO, Al-Kurdi A, Balla Al-Noor MA, et al. Prevalence and pattern of alternative medicine use: the results of a household survey. Ann Saudi Med. 2008;28:4.
4. Suleiman AK. Attitudes and beliefs of consumers of herbal medicines in Riyadh, Saudi Arabia. J Community Med Health Educ. 2014;4:1–7.
5. Fugh-Berman A, Ernst E. Herb–drug interactions: review and assessment of report reliability. Brit J Clin Pharmacol. 2001;52:587.
6. An overview on safety issues of interactions between traditional herbal medicines and pharmaceutical medicines| Western Sydney University ResearchDirect [Internet]. https://researchdirect.westernsydney.edu.au/islandora/object/uws:29501. Cited 7 Nov 2022.
7. Parveen A, Parveen B, Ahmad S, Parveen R. Challenges and guidelines for clinical trial of herbal drugs. J Pharm Bioallied Sci. 2015;7(4):329–33.
8. Vizirianakis IS, Spanakis M, Termentzi A, Niopas I, Kokkalou E. Clinical and pharmacogenomic assessment of herb-drug interactions to improve drug delivery and pharmacovigilance. In: Plants in traditional and modern medicine: chemistry and activity. 2010. p. 978–81.
9. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.
10. Pan HY, Wu LW, Wang PC, Chiu PH, Wang MT. Real-world evidence of the herb-drug interactions. J Food Drug Anal. 2022;30(3):316–30.
11. Skalli S, Bencheikh RS. Safety monitoring of herb-drug interactions: a component of pharmacovigilance. Drug Safety 2012;35(10):785–91.
12. Investigation of drug interactions | European Medicines Agency [Internet]. [cited 2022 Nov 7]. Available from: https://www.ema.europa.eu/en/investigation-drug-interactions.
13. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. 2004. https://apps.who.int/iris/bitstream/handle/10665/43034/9241592214_eng.pdf.
14. FDA warns consumers about health risks of herbal coffee products from Malaysia containing undeclared active pharmaceutical ingredients and milk | FDA [Internet]. [cited 2022 Dec 25]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-about-health-risks-herbal-coffee-products-malaysia-containing-undeclared-active.
15. FDA advises patients not to use Herbal Doctor Remedies medicines | FDA [Internet]. [cited 2022 Dec 25]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-not-use-herbal-doctor-remedies-medicines.
16. FDA Alert on "Healthy Beauty" Angel Formula Intended for Infants and Children by Moor Herbs | FDA [Internet]. [cited 2022 Dec 25]. Available from: https://www.fda.gov/food/alerts-advisories-safety-information/fda-alert-healthy-beauty-angel-formula-intended-infants-and-children-moor-herbs.
17. MedWatch: The FDA Safety Information and Adverse Event Reporting Program | FDA [Internet]. [cited 2022 Nov 7]. Available from: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.
18. Alghamdi W, Al-Fadel N, Alghamdi E, Alghamdi M, Alharbi F, Signal Detection and Assessment of Herb-Drug Interactions: SFDA Experience. 2023. [Online]. Available: https://www.authorea.com/users/602701/articles/633422-signal-detection-and-assessment-of-herbal-drug-interactions-sfda-experience. [Accessed 2023].
19. VigiBase | UMC [Internet]. WHO Programme for International Drug Monitoring. [cited 2022 Nov 7]. Available from: https://who-umc.org/vigibase/.
20. AdisInsight by scientists | Springer — International Publisher [Internet]. [cited 2022 Nov 7]. Available from: https://www.springer.com/gp/adis/products-services/adisinsight-databases?gclid=CjwKCAjwtp2bBhAGEiwAOZZTuEzAlLVGXCDRghpgzRxvQZyNxfiDtc0bbVmETBjDedFBbez4Vw7COxoCK-UQAvD_BwE
21. Natural Medicines Research Collaboration [Internet]. [cited 2022 Nov 7]. Available from: https://naturalmedicines.therapeuticresearch.com/.
22. Home - PMC - NCBI [Internet]. [cited 2022 Nov 7]. Available from: https://www.ncbi.nlm.nih.gov/pmc/.
23. Cochrane | Trusted evidence. Informed decisions. Better health. [Internet]. [cited 2022 Nov 7]. Available from: https://www.cochrane.org.
24. Van Hunsel, van der Kooi D, van de Koppel S, Kroes BH, Woerdenbag HJ. Analysis of reports on adversevdrug reactions related to herbal medicinal products and herbal supplements in the Netherlands received by the National Pharmacovigilance Centre Lareb. Drug Saf. 2022;45:651–61.
25. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother. 2007;41:674–80.

26. Hou XL, Takahashi K, Kinoshita N, Qiu F, Tanaka K, Komatsu K, et al. Possible inhibitory mechanism of Curcuma drugs on CYP3A4 in 1alpha,25 dihydroxy vitamin D3 treated Caco-2 cells. Int J Pharm. 2007;337:169–77.
27. Anuchapreeda S, Leechanachai P, Smith MM, Ambudkar S V., Limtrakul P ngarm. Modulation of P-glycoprotein expression and function by curcumin in multidrug-resistant human KB cells. Biochem Pharmacol. 2002;64:573–82.
28. Nayeri A, Wu S, Adams E, Tanner C, Meshman J, Saini I, et al. Acute Calcineurin Inhibitor Nephrotoxicity Secondary to Turmeric Intake: A Case Report. Transplant Proc. 2017;49:198–200.
29. Natural Medicines - Monograph Update: Turmeric Might Interact with Immunosuppressant [Internet]. [cited 2022 Nov 10]. Available from: https://naturalmedicines.therapeuticresearch.com/news/news-items/2017/march/monograph-update-turmeric-might-interact-with-immunosuppressant.aspx.
30. Egashira K, Sasaki H, Higuchi S, Ieiri I. Food-drug interaction of tacrolimus with pomelo, ginger, and turmeric juice in rats. Drug Metab Pharmacokinet. 2012;27:242–7.
31. Hansen TS, Nilsen OG. Echinacea purpurea and P-glycoprotein drug transport in Caco-2 cells. Phytother Res. 2009;23(1):86–91.
32. Drug Interactions: Echinacea. Medicines Complete (2022).
33. Probable etoposide interaction with echinacea. J. Diet. Suppl. 2012;9(2):90–5. https://doi.org/10.3109/19390211.2012.682643.
34. Chevallier A. Stockley's herbal medicines interactions (11th ed.). Pharmaceutical Press. 2023.
35. Necyk C, Ware MA, Arnason JT, Tsuyuki RT, Boon H, Vohra S. Increased bruising with the combination of long-chain omega-3 fatty acids, flaxseed oil, and clopidogrel. CPJ. SAGE Publications. 2013;146:93.
36. Budhraja V, Paul D. Warfarin and flax seed oil interaction and a mechanism for Polyunsaturated Fatty Acid and Warfarin interactions. 2009.
37. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. J Clin Pharmacol. 1995;35:209–19.
38. Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. J Clin Pharm Therap. 2002;27:391–401.
39. Shiyong Y, Yijia X, Peng Z, Chong L, Wuming H, Linchun L, et al. Ginkgo biloba extract inhibits platelet activation via inhibition of Akt. Integr. Med. Int. 2015;1:234–42.
40. Holden W, Joseph J, Williamson L. Use of herbal remedies and potential drug interactions in rheumatology outpatients. Ann Rheum Dis. 2005;64:790.
41. Haller C, Kearney T, Bent S, Ko R, Benowitz N, Olson K. Dietary supplement adverse events: report of a one-year poison center surveillance project. J Med Toxicol. 2008;4:84–92.
42. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic Ginkgo biloba ingestion. Neurology. 1996;46:1775–6.
43. Meisel C, Johne A, Roots I. Fatal intracerebral mass bleeding associated with Ginkgo biloba and ibuprofen. Atherosclerosis 2003;167:367.
44. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of Ginkgo biloba extract. N Engl J Med. 1997;336:1108.
45. Bebbington A, Kulkarni R, Roberts P. Ginkgo biloba: Persistent bleeding after total hip arthroplasty caused by herbal self-medication. J Arthroplasty 2005;20:125–6.
46. Werba JP, Misaka S, Giroli MG, Shimomura K, Amato M, Simonelli N, et al. Update of green tea interactions with cardiovascular drugs and putative mechanisms. J Food Drug Anal. 2018;26:S72–7.
47. Lexicomp: Interactions [Internet]. [cited 2022 Nov 10]. Available from: https://online.lexi.com/lco/action/interact.
48. Wang ZM, Bei C, Bo Z. Green consumption and the risk of stroke"A systematic review and meta-analysis of cohort studies. J Nutr. 2023;107:111936.
49. Taylor JR, Wilt VM. Probable Antagonism of Warfarin by Green Tea. https://doi.org/10.1345/aph.18238. SAGE Publications; 2016;33:426–8.
50. Phytochemical Constituents and Pharmacological Effects of Liquorice: A Review. [cited 2022 Nov 10]. Available from: https://www.researchgate.net/publication/328407685_Phytochemical_Constituents_and_Pharmacological_Effects_of_Liquorice_A_Review.
51. Janne H, Olavi U, Markku J. Effects of low-dose liquorice alone or in combination with hydrochlorothiazide on the plasma potassium in healthy volunteers. Blood Press. 2009;18(4):192–5.
52. Horwitz H, Woeien VA, Petersen LW, Jimenez-Solem E. Hypokalemia and rhabdomyolysis. J Pharmacol Pharmacother. 2015;6:98–9.
53. Heidemann HT, Kreuzfelder E. Hypokalemic rhabdomyolysis with myoglobinuria due to licorice ingestion and diuretic treatment. Klin Wochenschr; 1983;61:303–5.
54. Conn JW, Rovner DR, Cohen EL. Licorice-Induced Pseudoaldosteronism: Hypertension, Hypokalemia, Aldosteronopenia, and Suppressed Plasma Renin Activity. JAMA. American Medical Association 1968;205:492–6.
55. Chataway SJS, Mumford CJ, Ironside JW. Self-induced myopathy. Postgraduate Medical Journal. BMJ Publishing Group 1997;73:593.
56. Brouwers AJ, van Meulen J. Licorice hypertention also caused by licorice tea. Ned Tijdschr Geneeskd. 2001;145(15):744–7.
57. World Health Organization. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. [cited 2022 Nov 7]. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/43034/9241592214_eng.pdf. 2004.
58. Shaw D, Graeme L, Pierre D, Elizabeth W, Kelvin C. Pharmacovigilance of herbal medicine. J Ethnopharmacol. 2012;140:513–8.