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Systematic Review

Beyond the Silver Lining in Foods and Herbal Remedies: Updates on Toxicities and Interaction with Conventional Therapies-A Systematic Review

Samuel James Offor*

Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Uyo, Nigeria

***Corresponding Author:** Samuel James Offor, Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Uyo, Nigeria.

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Abstract

Globally, there is a tremendous increase in the use of herbal medicinal products and several food substances in the management and prophylaxis of several disease conditions. Although some of these remedies have potential benefits, there is an erroneous public perception that they are "natural" and so speculated to be devoid of adverse effects. However, the rise in the incidence of clinically significant interactions of herbs and food compounds with prescription drugs and overt-the-counter medications, including their toxicities has become an important public health concern. This systematic review aims at raising the awareness level about the preponderance of safety issues associated with concurrent administration of some herbal remedies and food compounds with conventional therapies. Online searches were carried out in the databases of PubMed, Medline and Google Scholar for publications using terms like "herb-drug interactions," "food-drug interactions," "phytotherapy," and "toxic effects of herbs and food compounds." Lateral searching via related citation (PubMed), checking reference lists of identified studies and narrative synthesis of included studies were performed. Adverse effects and interactions were reported between prescription drugs and some natural remedies and foods such as herbal teas, coffee, red wine, St. John's Wort, grapefruit, garlic, *Ginkgo biloba* and many others. By establishing safety issues associated with the sole use or combination of foods and herbal remedies with conventional drugs, practitioners can identify and manage potential risk of herb-drug interactions or toxicities. This will avoid the indiscriminate use of these products, thereby curtailing their toxicities and therapeutic failures in vulnerable individuals.

Keywords: *Herb-Drug Interaction; Food-Drug Interaction; Prescription Drug; Safety; Toxicities*

Introduction

Globally, there is a tremendous increase in the use of herbal medicinal products and several food substances in the management and prophylaxis of several disease conditions. Herbal medicinal remedy or product is defined as "any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations" [1]. Although some of these remedies have potential benefits, there is an erroneous public perception that that they are "natural" and so speculated to be devoid of adverse effects. Beyond the 'silver lining' (a metaphor depicting a sign of hope) of successfully using herbal remedies and food compounds for mitigation of otherwise difficult-to-treat disease conditions, their possibility of causing adverse effects and interacting with conventional drugs seems to belie the erroneous impression of

being totally harmless. Unlike conventional medicines, these products generally have multiple compounds, making their pharmacological characteristics and safety unpredictable [2,3]. Natural products contain pharmacologically active molecules potentially able to cause danger to human health [4]. The rise in the incidence of interactions of herbs and food substances with prescription drugs and over the counter medications, including their toxicities has become an important public health concern. The World Health Organization is currently promoting specific strategies for the prevention of these kinds of pharmacological interactions by establishing public policies that support the diffusion of knowledge on the concept [5,6]. To further tackle this conundrum, the regulatory agencies of Canada, the European Union and the USA have instituted the obligation to mention on the label of herbal products, their possible interactions with prescription drugs, in case of confirmed evidence [6-8]. Whereas there is documented evidence of herb-induced toxicities in developed countries based on robust pharmacovigilance programmes, information is sparse for the data-poor communities of sub-Saharan Africa, Asia and the Caribbean, where the contents of most of these herbal remedies are unregulated and unstandardized [9]. In Nigeria, most adverse effects associated with the use of herbal medicines are not reported to the regulatory body, National Agency for Food and Drug Administration and Control (NAFDAC) or national pharmacovigilance centers, which is an indication of inadequate monitoring of adverse effects [9].

Drug interactions occur when the pharmacological effect of one drug is altered by the presence of another drug or xenobiotic, which includes herbal medicine, food or drink bioactive components, or any other chemical agents [10]. If clinically significant, drug interactions may pose a risk for human health as they can affect therapeutic outcome and even cause life-threatening adverse drug reactions [10]. Recent studies have clearly shown that adverse events due to herbal remedies are relatively infrequent, if assessed for causality [11]. Nevertheless, the absence of evidence does not mean evidence of absence. There are few reports on pieces of evidence of adverse effects of some foods and herbal remedies.

Aim of the Study

This work aims at raising the awareness level on the possibility of rare but sometimes severe adverse effects from some foods and herbal products as well as the preponderance of safety issues related to their concurrent administration with conventional drugs.

Methodology

Database searching, search strategy and selection criteria

The methodology for this systematic review was carried out according to recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols [12]. Multiple online interactive searches in the databases of PubMed, Google Scholar and MEDLINE to identify relevant literature using terms such as "herb-drug interactions," "food-drug interactions," "phytotherapy," and "toxic effects of herbs and foods." Lateral searching via related citation (PubMed) and checking the reference lists of identified studies were carried out. Searched results were screened, and the titles and abstracts were read for eligibility. For all potentially eligible articles, full texts were obtained and inclusion and exclusion criteria applied to determine the suitability of the article to be included in this review. The quality of evidence was assessed according to the criteria of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group [13]. Finally, findings obtained from the selected studies will be summarized in a narrative synthesis.

Inclusion criteria, exclusion criteria and study designs

Studies assessing the concurrent use of herbs and foods with prescription drugs and/or over the counter medications were included. Studies evaluating the adverse effects of food compounds or herbal remedies used alone will also be included. If multiple reports were published from the same study, the most recent study was included. Articles were excluded if concurrent use of herbs and foods with contemporary therapy were not associated with toxic outcomes or interactions, and if the research articles were unavailable in English

language. The study designs included in this review are: (a). Quantitative research articles which may include clinical trials, comparative and observational studies; and (b). Case reports of adverse effects and interactions occurring between foods or herbs and conventional drugs. No limits were applied to the year of study.

Results and Discussion

Search Results: One hundred and seventy-eight (178) studies were found in the initial search. After screening of both titles and abstracts, 66 articles were excluded for being irrelevant (n = 47), nonavailability of full texts (n = 16), not available in English (n = 1), duplicates (n = 3). Further review of the full texts of the remaining 112 articles with strict application of the inclusion and exclusion criteria resulted in the exclusion of 14 articles, thus leaving 98 studies that were included in this review (Figure 1).

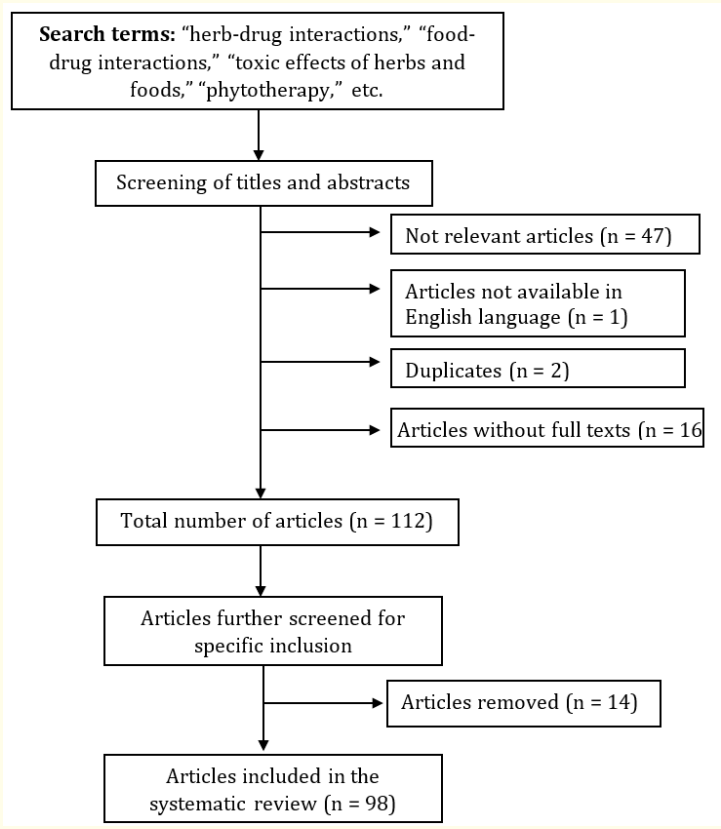

Figure 1: *Flow diagram of study selection PRISMA (Preferred reporting items for systematic reviews and meta-analyses).*

Drug-herb interactions

Several incidents have been reported about interactions between herbal remedies and conventional medicines. Phytomedicines implicated include evening primrose oil, St John's wort, *Ginkgo biloba*, *Aloe vera,* Garlic, *Aloe vera*, green tea, and many others.

Ginkgo biloba

Ginkgo is extracted from the leaves of the *Ginkgo biloba* tree. It has been postulated to increase cerebral blood flow, thus used for treatment of several conditions including post-thrombotic syndrome, peripheral vascular disease, confusion, difficulties with memory (thus used as a brain booster), anxiety, headache and tinnitus [14]. The bioactive components of *Ginkgo biloba* include the ginkgo-flavone glycosides or flavonoids (e.g. bilobetin, ginkgetin, sciadopitisin, quercetin) and the terpenoids (bilobalides and ginkgolides) [14,15]. serious adverse effects such as prolonged bleeding times and spontaneous subdural hematomas have been reported with *Ginkgo biloba*, due to its anti-platelet aggregating factor activity [14]. This bleeding episode has been reported to occur even in the absence of anti-coagulants. Some of the possible drug interactions of *Ginkgo biloba* involves its inhibition of platelet aggregation when simultaneously used with aspirin, acetaminophen, warfarin, ticlopidine, clopidogrel, and dipyridamole resulting in spontaneous bleeding [14,16]. However, controlled clinical trials in humans have refuted these anti-coagulant and anti-platelet case reports, hence, the need for their reappraisal [17]. *Ginkgo biloba* may also cause priapism (a prolonged and unwanted, persistent erection of the penis usually without sexual arousal) when combined with the antipsychotic drug risperidone [18], coma when used concurrently with the antidepressant, trazodone [19] and therapeutic failure when used with the anti-retroviral drug, efavirenz [20].

Ginkgo biloba has been reported to cause modest reduction in omeprazole blood levels. Other proton pump inhibitors may likely be similarly affected [21]. Other reports also indicted it with decreased tolbutamide blood concentration, decreased saquinavir blood concentration and increased talinolol blood concentration. There has been a report of fatal seizure potentiation with *ginkgo biloba* in the presence of anticonvulsant medications, phenytoin and valproic acid [14,17]. While many of the interactions are devoid of serious clinical consequences, some of them require extreme watchfulness.

Aloe vera

Aloe vera mucilage contains mostly anthraquinones and used as laxative, anti-inflammatory (in dermatologic conditions), antidiabetic and for anti-hyperlipidaemic purposes [4,17,22]. Incident of blood loss occurring during surgery due to possible interaction between *A. vera* and the anaesthetic, sevoflurane has been reported [23]. Both sevoflurane and *A. vera* are thought to inhibit platelet aggregation and may have additive effects [17].

St. John's wort

St. John's wort (*Hypericum perforatum* L.; family Clusiaceae) is a popular yellow flowering, perennial, medicinal herb native to Europe. The name is derived from its traditional flowering and harvesting on 24th June, the birthday of John the Baptist popularly known as St. John's Day [24,25]. It has been used for the treatment of depression [24]. It is credited as the most studied herbal supplement in the world [25], and the herb involved in most herb-drug interactions, hence adequate caution is required when used concurrently with other drugs so as to minimize its potential interaction with conventional drugs [17,26]. St. John's wort contains several bioactive compounds, with hyperforin as the main mediator of its anti-depressive activity. Other bioactive components include hypericin, pseudohypericin, and the flavonoids quercetin, quercitrin and I3, II8-biapigenin [24].

Concurrent use of St. John's wort with immunosuppressants (e.g. cyclosporine), antiretroviral drug (indinavir), cardiac glycoside (e.g. digoxin) or the antineoplastic agent (e.g. irinotecan and imatinib) may result in reduced plasma concentrations of these drugs [17,27-29]. It decreases blood concentration of alprazolam and amitriptyline. The American society of Anaesthesiologists cautions that St. John's wort be discontinued 2 - 3 weeks prior to surgery due to delayed emergence and cardiovascular collapse when used with general anaesthetics [24,30]. Studies have reported unwanted pregnancies with co-administration of St. John's wort and oral contraceptives as a result of alteration in the pharmacokinetics of these pills, leading to reduction in their efficacies, and increased incidents of breakthrough

bleeding [20,31,32]. Decreased blood concentrations of bupropion, fexofenadine, gliclazide, methadone, verapamil, simvastatin, rosuvastatin, theophylline, and zolpidem have also been reported when co-administered with St. John's wort [24]. It also increases warfarin clearance, thereby decreasing its anti-coagulant effect [24,33].

Green tea (*Camellia sinensis*)

Green tea is usually taken as a beverage and as herbal remedy [17,22]. It has been shown to decrease folate blood concentration when co-administered with folic acid [17,34]. It is also reported to increase the plasma level of statins [17,35], and postulated to reduce the anticoagulant effect of warfarin [17], probably due to its vitamin K content.

Garlic (*Allium sativum*)

Garlic is widely used as a condiment and a dietary supplement [24]. Its major bioactive compounds include flavonoids, organosulfur compounds, sapogenins, saponins, selenium compounds and fructosamines [36]. The flavonoids contained in garlic which show good antioxidant potentials include apigenin, quercetin, nobiletin, tangeretin, rutin, allixin, myricetin and bergamottin [36]. The chemical constituent, alliin is enzymatically converted to allicin (the major garlic component). Allicin is which is chemically unstable is converted to many other organosulfur compounds like disulfide, diallyl trisulfide and diallyl sulfide which are ultimately responsible for the pharmacological effects of garlic [24,37]. Garlic has hypolipidaemic, antihypertensive, antiatherogenic, fibrinolytic, anticarcinogenic, immunomodulatory, antimicrobial and hypoglycemic properties [38]. Some reports have it that garlic may influence platelet function and blood coagulation, resulting in bleeding when administered with the anticoagulant warfarin. However, this has not been confirmed by controlled clinical trial [17].

Evening primrose (*Oenothera biennis*)

Evening primrose has been used for treatment of premenstrual syndrome, and for alleviating menopausal symptoms. The oil is used externally for treatment of dermatological diseases, and internally for prophylaxis of atherosclerosis [17]. It has been reported to cause seizures when given concomitantly with fluphenazine due to its lowering of seizure threshold by gamalenic acid present in the oil [17].

Other herbs with potential drug interactions

Other herbs that have been reportedly involved in drug interactions include Goldenseal (*Hydrastis canadensis*), popularly found in North America used for treatment of gastrointestinal disturbances, dermatological diseases, urinary disorders, and infections [39]. Its main bioactive constituent, berberine is a potent inhibitor of CYP3A4 and has been reported to increase the bioavailability of cyclosporin in patients with renal transplant [40]. Another herb, Licorice (*Glycyrrhiza glabra*), mostly used for treatment of peptic ulcer and catarrh is known to increase the plasma concentration of prednisolone when given concurrently [17]. American Ginseng (*Panax quinquefolius*) was reported to reduce the anticoagulant efficacy of warfarin [41]. Valerian root (*Valeriana officinalis*) commonly used as a sleep aid which was combined with passion flower (*Passiflora incarnata*) was reported to cause dizziness, throbbing and muscular fatigue in a patient given lorazepam. Additionally, acute delirium was reported in a patient taking loperamide while also on herbal combination of valerian root and St. John's wort [42].

Drug-food interactions

Several food sources, including beverages, fruit and vegetable juices, though seemingly innocuous contain bioactive compounds capable of interacting with conventional drugs when used together. About 5000 phytochemicals have been found in fruits and vegetables, although a large proportion are yet to be discovered. This array of complex biochemically active constituents makes their interactions with drugs more unpredictable and challenging [11].

Grapefruit juice

Grapefruit juice and grapefruit pulp have been reported to have more than forty drug interactions in human being [11,43]. Grapefruit juice when given concurrently with lovastatin increased the bioavailability of lovastatin [44]. Grapefruit juice cause inhibition of CYP3A4 leading to development of adverse effects, myopathy and rhabdomyolysis [11]. There is also a case report of statin-related rhabdomyolysis caused by grapefruit consumption. Rhabdomyolysis is a rare but very serious adverse effect seen with statin therapy, that can result in kidney failure and death. In this scenario, the metabolism of simvastatin was altered due to CYP3A4 inactivation by the grapefruit, resulting in toxic level of simvastatin [11,45]. However, statins that are not substrates for the same CYP, such as rosuvastatin, are unlikely to have this drug interaction [11]. Other drugs known to have clinically relevant interaction with grapefruit juice are cyclosporine, carbamazepine and the antiarrhythmic drug amiodarone [46]. The bioactive components in grapefruit juice responsible for drug interactions include furanocoumarins, namely, bergamottin and 607 0 -dihydroxybergamottin [47], and also naringin, which can inhibit organic anion transporting polypeptide (OATP1A2) activity [48].

It is postulated that grapefruit juice can reduce the levels of CYP3A4 by 47% as early as four hours after consumption, and these effects are persistent in the intestinal and liver cells at least 24h after ingestion. Hence grapefruit juice, even without simultaneous administration with the drug, can result in drug interaction or alteration in metabolism of any CYP3A4 substrate for longer periods after consumption [49]. This can be seen in typical example of drug interaction involving the immunosuppressant, tacrolimus, where a prolonged increase in the body level of tacrolimus, e.g. from 4.7 ng/mL to 47.4 ng/mL, happened one week after the last grapefruit juice intake (250 mL, 4 times a day for 3 days). This resulted in the patient developing severe headache and nausea, and fortunately without nephrotoxicity [46,50]. Since it is difficult to predict the interaction of grapefruit juice with different orally given drugs, it is better to avoid taking grapefruit with drugs that are substrates for an intestinal CYP3A4 and/or P-glycoproteins, particularly for drugs with narrow therapeutic index and a poor oral bioavailability due to the high first-pass effect mediated by CYP3A4; because even a single consumption of grapefruit juice may result in drug toxicity. Other factors such as the concentration/amount of the grapefruit and interindividual variability of intestinal CYP3A4 activity may also contribute to the severity of the adverse effect [11,29,51].

Cocktail of juices

A cocktail of fruit juices from oranges, bananas and prunes, or combinations of vegetable juices like carrot and tomato juices, contain very high levels of potassium. Hence when taken with potassium-sparing diuretics (e.g. spironolactone, triamterene) or angiotensin-converting enzyme inhibitors (e.g. ramipril), particularly in patients with kidney disease and hypoaldosteronism, could result in life-threatening hyperkalaemia [11,52].

Soybean (*Glycine max* (L.) Merr.)

Soy beans (also known as Soya bean is an important food legume, very rich in phytoestrogens anecdotally used for treatment of menopausal symptoms and prevention of heart disease and cancer [39,53]. Decreased international normalized ratio, INR has been reported in a patient taking warfarin with soy beans milk [54].

Coffee (*Coffea arabica*)

There are more than 80 species of coffee identified worldwide, but *Coffea arabica* and *Coffea canephora* are the major two economically important species [55]. It is the most widely consumed beverage in the world. Globally, about 80% of the population consumes coffee and other coffee product daily, and this number rises to 90% among North American adults [55]. The natural alkaloid, caffeine (a methylxanthine), is the most important bioactive component of coffee known for its ability to stimulate the central nervous system (CNS)

[55]. Clinically significant pharmacokinetic interaction that occurs between coffee and some over-the-counter and prescription medications are attributable to its major constituents, mostly caffeine and chlorogenic acid [56]. Coffee can affect drug absorption by changing the gastrointestinal pH, dissolution profile, sink condition of the gastrointestinal membrane and blood, gastrointestinal emptying time, formation of complex, and through inhibition of glucose-6-phosphatase [55].

In Canada, a study carried out in humans reported that the plasma concentration of the antihypertensive agent, felodipine was significantly increased when taken with caffeine. It was postulated that the increased absorption of felodipine might be due to increased rate of gastric emptying by caffeine [57].

Another case report found that drinking coffee within one hour after taking the thyroid medication, Levothyroxine (L-T4) can significantly lower levothyroxine absorption. It was observed by the investigators that increased thyroid-stimulating hormone (TSH) secretion was a feedback mechanism for lowering levothyroxine concentration in the blood due to routine drinking of coffee [58]. Decrease in absorption of levothyroxine although mostly seen with coffee, may also occur when the drug is taken with caffeinated tea, hot chocolate, or caffeinated soft drinks [59].

Other foods with potential drug interactions

Red yeast rice which is produced by fermentation of washed and cooked rice using the fungus *Monascus purpureus* has been used to lower blood cholesterol [39]. In one case report, the rice which is known to cause myopathy even when given alone [60], was suspected to cause rhabdomyolysis in patient with renal transplant taking cyclosporine [61].

The polyphenol, resveratrol present in red grapes (*Vitis vinifera*) used in producing red wine is an inhibitor of CYP3A4. In a randomized cross-over study of volunteers, Californian red wine decreased bioavailability of cyclosporine [62]. Pomelo juice was reported to increase the AUC and Cmax, while decreasing the elimination half-life of cyclosporine [63] and also increased tacrolimus blood levels in patient undergoing renal transplant [64].

A schematic diagram showing some herb/food - drug interactions is shown in figure 2.

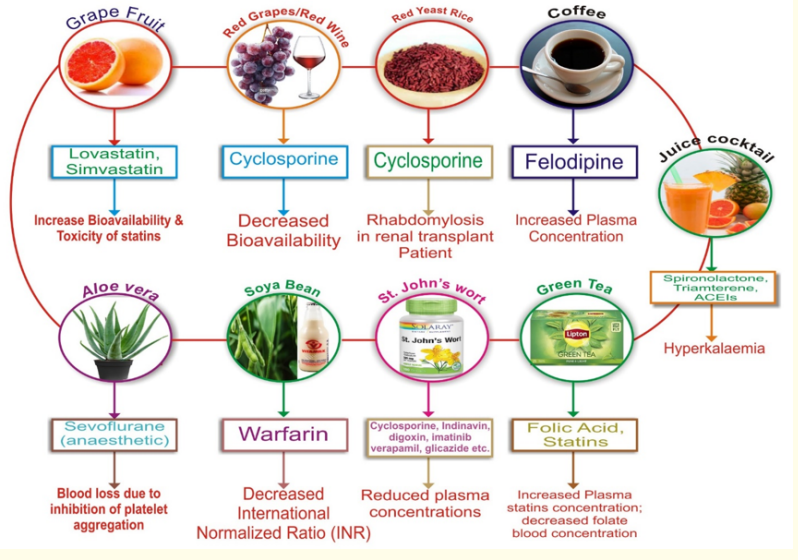

Figure 2: *Schematic diagram showing some herb/food-drug interactions.*

Some toxicities associated with the use of herbs and food substances only

Although the overall risk to public health appeared to be low, some traditional remedies and food substances could be associated with a number of potentially serious adverse effects, and several papers have reported the adverse effects associated with the use of phytomedicinal products [11,65]. The European Project PlantLIBRA (Plant Food Supplements: Levels of Intake, Benefit and Risk Assessment, Project no. 245199; http://www.plantlibra.eu) aims at fostering the safe use of food supplements-containing plants or botanical preparations by increasing science-based decision-making by researchers, regulators, and food chain operators [11]. Adverse effects have been reported with derivatives from green tea leaves (*Camellia sinensis* (L.) Kuntze and involved mainly acute hepatotoxicity. Patients exhibited clinical symptoms with different severity ranging from a mild elevation of serum aminotransferase levels to fulminant hepatitis that requires liver transplantation [11,66-68]. The types of preparation implicated in the adverse effects were hydroalcoholic extract and aqueous extract of green tea, taken as tea or in capsules [11,66]. Bioactive constituents mostly implicated in the hepatotoxic side effect of green tea are catechins and their gallic esters [11]. This side effect is not seen with fermented tea (black tea), in which the content of catechins is significantly reduced [11].

Adverse effects have also been reported with the consumption of *Cinnamomum verum* J. Presl (*Cinnamomum zeylanicum* cinnamon) in cinnamon-flavoured beverages, candies and chewing-gum. One case of intoxication was seen in a child [11]. The adverse effects involved stomatitis with swelling and burning of lips, tongue and cheeks, and ulceration [69]; hyperkeratotic plaques covering majority of the dorsal and lateral tongue and involves the buccal mucosa [70]; and contact allergy [71]. Adverse effects have also been reported with the consumption of *Glycine max* (L.) Merr. (soybean) used in several foods and products, such as soy 'milk', paediatric formulas and lecithin. The adverse effects involve allergic reactions and hormone-like activity from soybean [72]. The pseudo-hormonal side effects have been observed in both females and males and include uterine fibroids [73], endometriosis [74], gynaecomastia [75], and reproductive disorders [76].

Hypericum perforatum L. (St John's wort) when used alone has been reported to cause convulsions and confusion [77], manic attack [78], hypertension [79], sexual dysfunction [80], serotonin syndrome-like symptoms with anxiety, tachycardia and nausea and, a five-fold increase in transaminases [81]. *Vitis vinifera* L. (grape) has been reported to cause allergic reactions. This includes urticaria, oral syndrome, angioedema, hypotension, respiratory distress, anaphylaxis [11]. Other toxicities associated with the use of phytomedicines include hepatotoxicity due to pyrrolizidine alkaloids-containing plants [82], cardiotoxicity and neurotoxicity due to Aconitum alkaloids [83], lethal cardiovascular adverse effects associated with *Ephedra sinica*, whose sales have since been prohibited by the Food and Drug Administration in 2004 [84]. Siberian ginseng (*Eleutherococcus senticosus*) was associated with neonatal hirsutism [4].

Mechanisms of herb/food-drug interactions

Herb or food interactions with drugs are predicated on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. Pharmacokinetic interactions are the results of altered absorption, interference in pattern of distribution as well as alterations and competition in the metabolic and excretory pathways which eventually affects the plasma drug concentration, while pharmacodynamic involves drug interactions at receptor sites [85]. The major mechanism of pharmacokinetic interaction is either through the induction or inhibition of intestinal and hepatic metabolic enzymes, especially the CYP enzyme family e.g. the cytochrome P450 enzymes. The CYPs are the most important phase I drug-metabolizing enzyme system. The second mechanism involve similar effect on drug transporters and efflux proteins, notably the p-glycoproteins [85]. Polymorphisms in the genes for P-glycoprotein and CYP enzymes may affect the interactions mediated through these pathways [86]. P-glycoproteins are found in the intestine, liver and kidney. They perform important function in the absorption, distribution, or excretion of drugs, likely limiting the cellular transport from intestinal lumen into epithelial cells, as well as enhances the excretion of drugs through hepatocytes and renal tubules into the adjacent luminal space [24]. Several examples of pharmacokinetic interactions between conventional drugs and herbs or food compounds exist in literature. A typical

example of great public health importance is that of St. John's wort which can alter the plasma concentration of several drugs metabolized by cytochrome P450, and/or are transported by P-glycoproteins [17,24]. Bioactive compounds present in foods and herbs, just like drugs act as substrates of metabolizing enzymes. Hence, induction or inhibition of relevant metabolizing enzymes can affect the pharmacokinetics of drugs and may require contraindications by health workers.

Pharmacodynamic interactions on the other hand may involve additive (or synergetic) effect, in which case the herbal medicines potentiate the pharmacological/toxicological action of contemporary drugs, or antagonistic, that is a situation in which the herbal medicines reduce the efficacy of contemporary drugs. Interactions of herbal products with warfarin are classical examples of pharmacodynamic interactions [17]. Hypothetically, increased anticoagulant effects could be expected when warfarin is administered concurrently with coumarin-containing herbs known for their anticoagulant activities or with antiplatelet herbs. On the flip side, vitamin K-containing herbs can antagonize the effect of warfarin [17]. Mechanism of adverse effect of herbs or food compounds such as hepatotoxicity may include bioactivation of CYP, oxidative stress, mitochondrial injury, and apoptosis [24].

Conclusion

Several studies have alluded to the existence of potentially significant toxicities and interactions between herbal preparations or food compounds with conventional drugs attributable to one or more of their bioactive constituents. Although many of these adverse effects and interactions lack serious clinical consequences, a number of them calls for extreme vigilance. To achieve the maxim of rational and safe use of natural remedies either alone or in combination with prescription drugs and over-the-counter medications, it is important for clinicians, pharmacists, nutritionists and other healthcare professionals to be aware of growing evidence-based approach in disease therapy and prophylaxis. Additionally, highlighting the potential adverse effects and drug interactions of culpable herbal medicinal ingredients and food compounds on drug packages may help prevent harmful incidents in vulnerable individuals.

Conflict of Interest

Author declares no conflict of interest.

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