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Chapter

The Clinical Importance of Herb-Drug Interactions and Toxicological Risks of Plants and Herbal Products

Cigdem Kahraman, Zekiye Ceren Arituluk and Iffet Irem Tatli Cankaya

Abstract

Approximately 70% of the world's population has been using medicinal herbs as a complementary or alternative medicine that has grown tremendously in both developed and developing countries over the past 20 years (World Health Organization Drugs Strategy 2002–2005). This increase in consumer demand for medicinal plants continues, although scientific data are rare to create safety and efficacy profiles. Its popularity is also related to easy availability, cost-effectiveness leading to better purchasing power, and various factors that perceive that they are generally safe. Herbs are often administered simultaneously with therapeutic drugs for the treatment of major ailments, and herb-drug interactions (HDIs) increase their potential. The main routes proposed for HDIs include cytochrome P450 (CYP450)-mediated inhibition or induction and transport and flow proteins. In our review, we highlighted herbal medicines used for the treatment of various diseases with pharmacokinetic, pharmacodynamic analysis and case reports together with their adverse effects and herb-drug interactions. Therefore, this review can be used as a quick reference database for physicians and healthcare professionals involved in therapy, aiming to maximize clinical outcomes by reducing the negative and toxic effects of plants along with avoiding herb-drug interactions.

Keywords: herbs/plants, herbal products, natural products, drugs, interactions, toxicity

1. Introduction

Herbal products are considered the best choice as complementary medicine in western countries, especially in the United States and Europe. Annual sales of dietary herbal supplements in the United States increase 6.8% year over year. In addition, China and India are the top export countries, while Hong Kong, Japan, the United States, and Germany are the leading importers. The Confederation of Indian Industry (CII) presented that the market size of the Ayurvedic industry in the country is $ 4.4 billion, and the total market size of the Indian health industry is $ 11.8 billion. There has been an increase in demand for "complementary" medicines, including those of plant origin. In addition, there is a significant increase in the self-administration of herbal medicines among the public. In the context of the

growing demand and use of herbal medicines for patients and the public, and the subsequent interests of the regulatory authorities, comprehensive research on the safety and effectiveness of herbal products, including the possibility of interactions when simultaneous application is required, should be encouraged. This is because all herbal medicines and dietary supplements are a complex mixture containing multiple active phyto-components that increase the possibility of herb-drug interaction (HDI). Most people who consume herbal products and supplements do not show this to their pharmacist or doctor, thereby increasing the likelihood of HDI being identified and resolved over time. However, data from recent studies show that there is potential for serious interaction between some commonly used herbs/herbal products and commonly used standard medications [1].

In our review, we highlighted herbal medicines used for the treatment of various diseases with their adverse effects and herb-drug interactions, and stated recommendations for proper use of plants that might prevent possible risks for future incidents.

2. Toxicological risks of plants and herbal products

General risks associated with herbs and/or herbal products include:

- Misidentification without assigning with Latin names. Possible causes of misidentification include contamination of cultivated plants with weeds, and resembling plants mistaken for herbs collected in the wild.

- Contamination with harmful substances such as heavy metals, polycyclic aromatic hydrocarbons, dioxins, as well as natural toxins or microorganisms.

- Interaction with other drugs, such as antagonism or synergism, and medical tests that potentially lead to misdiagnosis.

- Adulteration with other medicinal drugs.

- Intrinsic toxicity caused by the presence of natural toxins, such as aristolochic acids [2].

2.1 Nephrotoxicity

The drug or toxin that causes kidney damage when exposed to a certain level cannot pass the excess urine, and the waste product is what is called nephrotoxicity. In this case, there is an increase in blood electrolytes, such as potassium and magnesium. This situation begins temporarily but can be serious if it is not detected before. Blood urea nitrogen (BUN) test and creatinine levels in the blood are two simple tests called as kidney function tests used to detect the nephrotoxicity. For healthy individuals, the normal levels of BUN and creatinine are between 10–25 mg/dl and 0.7–1.4 mg/dl, respectively. The following factors may increase these values:

a. Dehydration.

b. Obstruction of blood flow to or from kidney caused by a tumor, stone, or irregular heart rhythms.

c. Nephritis or urinary tract infection.

d. The aftermath of diseases such as diabetic neuropathy, congestive heart failure, and enlarged prostate gland in man.

e. Gastrointestinal bleeding.

f. Prolonged hypotension.

g. Protein-rich diets.

h. Radiocontrast dye injected intravenously to improve visibility.

i. Drug toxicity with some chemotherapeutics (carboplatin, carmustine, cisplatin, methotrexate, and mitomycin) and biological therapeutic agents (interleukin-2 and interferon-alpha), antibiotics (amphotericin B, gentamicin, and vancomycin), NSAIDs (ibuprofen), diuretics (furosemide), and ACE inhibitors (captopril, benazepril, and enalapril).

j. Nephrotoxicity after taking herbal medicine.

The cause of nephrotoxicity after taking herbal medicine may be the addition of toxins during careless preparation, addition of adulterants, heavy metals, and some pharmaceutical products intentionally reducing costs or increasing effectiveness [3].

About 50 plants were related to kidney damage case reports published in PubMed in the last 50+ years (from 1966 to May 2016). Herbs include *Aristolochia fangchi* Y.C.Wu ex L.D.Chow & S.M.Hwang, *Artemisia herba-alba* Asso, *Callilepis laureola* DC., *Cupressus funebris* Endl., *Ephedra sinica* Stapf, *Hypericum perforatum* L., *Taxus celebica* (Warb.) H.L.Li, *Tribulus terrestris* L., and *Tripterygium wilfordii* Hook.f. *Aristolochia* species containing aristolochic acid, *Aristolochia fangchi*, had the highest number of publications (not actual cases) [4].

2.2 Hepatotoxicity

Hepatotoxicity ("Hepar" means liver and "Toxicon" means poison in ancient Greek) implies liver damage caused by medication, chemical, herbal, or dietary supplements. Stomach pain, vomiting, nausea, chance in urine and stool color, rash, jaundice, frequent tiredness, weakness, fatigue, and fever are the main symptoms of the damage. Some liver function tests performed on blood samples allow detecting hepatotoxicity in the laboratory. These tests include alanine transaminase test (normal range 7–55 U/l), alkaline phosphatase test (normal range 45–115 U/l), albumin test (normal range 3.5–5.0 g/dl), aspartate transaminase test (normal range 8–48 U/l), and bilirubin test (normal range 0.1–1.2 mg/dl). Increased ALT, ALP, AST, and bilirubin and decreased albumin levels demonstrate hepatotoxicity. The levels of ALP also increase during pregnancy [3].

The causes of liver damage are both hepatocellular and extracellular mechanisms such as hepatocyte disruption, transport protein disruption, T-cell activation, hepatocyte apoptosis, disruption of mitochondria, injury of bile duct, drug toxicity, and drug interaction [3].

Drug toxicity mechanisms: drugs are the main cause of hepatotoxicity. About 900 drugs, toxins, and herbs have been reported for hepatotoxicity. There are two types of drug reactions: the first is the reaction that directly affects the liver, called internal drug reactions; and the other is the reaction that mediates the immune response, called idiosyncratic drug reactions. In the first category, the drug itself or its metabolite produces a dose-dependent injury, such as paracetamol and carbon

tetrachloride. In the second category, hypersensitivity reactions, for example, phenytoin reaction, cause an immunoallergic or metabolic idiosyncratic reaction due to fever, rash, eosinophilia and indirect drug reaction for a short time. The second reaction type response rate is variable, for example, halothane [3].

Drug interaction mechanisms: when some drugs are taken at the same time, they react together and cause liver damage. For example, the combination of tylenol with INH, histamine, laniazide, and nydrazide can be hepatotoxic [3].

When hepatotoxicity caused by herbal drug intake is discussed, case rates are often reported. The severity of toxicity varies greatly between mild hepatitis and acute liver failure. The scoring system for allopathic drugs can be evaluated, but not suitable for herbal medicines and needs validation. Many Ayurvedic and Chinese herbal medicines are reported to cause hepatotoxicity. The main hepatotoxic herbs are *Cimicifuga racemosa* (L.) Nutt., *Larrea tridentata (*Sessé & Moc. ex DC.) Coville, *Scutellaria baicalensis* Georgi, *Scutellaria lateriflora* L., *Teucrium chamaedrys* L., etc. [3].

2.3 Cardiotoxicity

Cardiotoxicity is a term used for damage to the heart or change heart functions. It is a condition where there is a change in the electrophysiological function of the heart or damage to the heart muscle, weakening the heart and causing poor blood circulation. This can be detected by symptoms such as dry, unproductive cough; inflammation in the ankles, hands, feet, and neck vessels; irregular heartbeat; tachycardia; cardiomegaly; weakness; dizziness; etc. [3].

Herbal drugs that have a direct effect on the heart include medicine prepared from plants such as *Aconitum napellus* L., *Atropa belladonna* L., *Catharanthus roseus* (L.) G.Don, *Digitalis purpurea* L., *Ephedra distachya* L., *Glycyrrhiza glabra* L., *Mandragora officinarum* L., etc. [3].

2.3.1 Potential precautions of plants on hypertension

Herbal products are widely used in the general population and many are encouraged for the natural treatment of hypertension. Patients with hypertension often prefer to use these products in addition to or instead of pharmacological antihypertensive agents. Due to the frequent use of herbal products, both consumers and healthcare providers should be aware of the major issues surrounding these products and factors affecting both effectiveness and damages (**Table 1**) [5].

Herbal/natural products for evidence of benefit	**Herbs/herbal products for evidence of harm**	**Causes**
Coenzyme Q10	*Ephedra* spec. (Ephedra)	Cardiac effects, hypertension, palpitations, tachycardia, stroke, seizures
Fish oil	*Citrus* × *aurantium* L. (Bitter orange)	Blood pressure increases occur in healthy people
Allium sativum L. (Garlic)	*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Siberian Ginseng)	Hypertension, tachycardia, palpitations
Vitamin C	*Glycyhrriza glabra* (Licorice)	Mineralocorticoid excess syndrome, subsequent hypertension

Table 1.
Herbal/natural products in hypertension for their benefits and disadvantages.

2.4 Neurotoxicity

The physical brain damage occurred by exposure to neurotoxin is stated as neurotoxicity. Neurotoxin is a substance that causes changes in the nervous system activity by disrupting or killing neurons. Neurotoxicity symptoms are generally emotional disorders, visual impairment, extremity failing, sexual dysfunction, headache, and behavioral alteration. *Atropa belladonna*, *Brugmansia* species, *Catharanthus roseus*, *Cannabis sativa* L., *Conium maculatum* L., *Coscinium fenestratum* (Goetgh.) Colebr., *Datura stramonium* L., *Hyoscyamus niger* L., and *Papaver somniferum* L. are the common medicinal herbs that have potential neurotoxic effects [3].

2.4.1 Psychiatric and neurological adverse effects

Psychiatric and neurological patients often try herbal medicines assuming they are safe. Numerous case reports include various adverse events such as cerebral arteritis, cerebral edema, delirium, coma, confusion, encephalopathy, hallucinations, intracerebral hemorrhage and other cerebrovascular accidents, movement disorders, mood disorders, muscle weakness, paresthesia, and seizures. Some deaths have been recorded. Misuse is caused by toxicity of herbal ingredients, contamination and adulteration, and herb-drug interactions [6] (**Table 2**).

Herbs	Adverse effects	Potential drug interactions
Panax ginseng C.A.Mey.	Insomnia, vaginal bleeding, mastalgia, mania	Phenelzine, hypoglycemic drugs
Valeriana officinalis L. (Valerian)	Headache, GI symptoms, hangover	Other CNS depressants
Datura stramonium (Jimson weed)*	Ataxia, blurred vision, disorientation, other cholinergic signs	Other anti-cholinergic agents
Glycyrrhiza glabra (Licorice)	Mineral corticoid effects	Antihypertensives, corticosteroids, digoxin
Passiflora incarnata L. (Passionflower)	Nausea, drowsiness, ventricular tachycardia	Other CNS depressants
Mentha pulegium L. (Pennyroyale)	GI symptoms and cramps, confusion, hallucination, liver failure	Inhibitors of cytochrome P-450 system
Piper methysticum G.Forst. (Kava)*	GI symptoms, restlessness, allergies, hepatitis	Other CNS depressants
Ephedra sinica (Ma Huang)*	Anxiety, confusion, insomnia, psychosis	Other CNS-stimulants, beta-blockers, MAO-inhibitors, phenothiazines, theophylline
Ginkgo biloba L.	GI symptoms, allergies, headache, dizziness, bleeding	Anticoagulants
Tripterygium wilfordii (Thunder God Vine)*	Dryness of mouth, nausea, GI symptoms, leukopenia	Not known
Eucalyptus sp.	Cyanosis, delirium, GI symptoms	Not known
Hypericum perforatum (St. John's wort)	GI symptoms, allergies, fatigue, anxiety	Serotonin reuptake inhibitors, hepatic enzyme inducer
Aconitum sp. (Aconite)*	Acidosis, bradycardia, diarrhea, hypokalemia	Antiarrhythmics, antihypertensives

**Although we know the unconscious use of plants or their products, some of the plants given in the table are potent plants that are undesirable to be used in phytotherapy, but they are generally used in Traditional Chinese Medicine.*

Table 2.
Herbal remedies implicated in causing neurological adverse effects [6].

2.5 Skin toxicity

Cutaneous toxicity is a term used for a pronounced negative effect such as skin irritation, inflammation, or rashes of the epidermal growth factor receptor caused by exposure to a plant, chemical, or environmental factor. Skin consisting of a layer of dead cells and several layers of living cells is the largest organ and a defensive barrier of the body. When irritant influences into the skin, the living cells react due to cause inflammation or dermatitis. Inflammation consists of four parts including redness, pain, heat, and swelling. Skin toxicity can be detected easily as the reaction is observed immediately. The most common sources of skin toxicity are food and cosmetics, and others are medicated lotions, balms, creams, inhalers, and essential oils. Various herbal ingredients are available in all the cosmetics and medicinal products mentioned above. Types of skin sensitization reactions include:

Primary irritant dermatitis: it is a direct irritation of the skin, such as redness, itching, pain, blusters, peeling, or open wounds. Primary irritant dermatitis may be caused by plants such as, *Asclepias syriaca* L., *Cannabis sativa*, *Dieffenbachia amoena* Bull., *Digitalis purpurea*, *Ficus carica* L., *Hevea brasiliensis* (Willd. ex A.Juss.) Müll. Arg., *Narcissus pseudonarcissus* L., *Primula veris* L., *Ranunculus acris* L., *Ricinus communis* L., *Tulipa gesneriana* L., etc. Common foods such as *Agaricus bisporus* L., *Apium graveolens* L., *Brassica rapa* L., *Cucumis sativus* L., *Daucus carota* L., *Pastinaca sativa* L., *Petroselinum crispum* (Mill.) Fuss, and *Solanum lycopersicum* L. can also cause primary irritant dermatitis.

Allergic contact dermatitis: it is a real allergic response and varies from person to person. *Toxicodendron diversilobum* (Torr. & A.Gray) Greena and *Toxicodendron rydbergii* (Small ex Rydb.) Greene, *Allium cepa* L., *Allium sativum, Anacardium occidentale* L., *Apium graveolens, Cedrus deodara* (Roxb. ex D.Don) G.Don, *Dendranthema grandiflorum* (Ramat.) Kitam., *Hedera helix* L., *Marchantiophyta* species, *Narcissus pseudonarcissus*, *Primula vulgaris* Huds., *Pinus sabiniana* Douglas, *Toxicodendron vernix* (L.) Kuntze, and *Tulipa gesneriana* are the most common plants that produce allergic contact dermatitis.

Photosensitization dermatitis: it is a cutaneous toxic response caused by exposure to sunlight when a photosensitizer (sunlight sensitive compound) is present in the body and can be detected by sunburn-like reactions in pigment-free areas. Plants such as *Agave lechuguilla* Torr., *Bassia scoparia* (L.) A.J.Scott, *Hypericum* species (St John's wort), *Lantana camara* L., *Tetradymia* species, and *Tribulus terrestris* cause photosensitive dermatitis [3].

There is another type of phototoxic photosensitization caused by contact with some plants. Such a reaction occurs when a photoactive chemical produced by plants touches the skin, and is absorbed and activated by sunlight. Intensity varies depending on time and exposure amount. *Anethum graveolens* L., *Apium graveolens* L., *Brassica oleracea* L., *Citrus aurantiifolia* (Christm.) Swingle, *Daucus carota*, *Ficus carica*, *Hypericum perforatum* (St. John's wort), *Petroselinum crispum*, and *Ranunculus acris* are reported to produce contact photosensitization [3].

3. Contamination of herbal medicines by tropane alkaloids

Tropane alkaloids that have been known as toxic and hallucinogenic are mainly seen in Solanaceae plants (*Atropa belladonna*, *Hyoscyamus niger*, *Datura stramonium*, etc.). All over the world, anticholinergic poisoning is observed due to the contamination of herbal teas and plants with tropane alkaloids. Tropane alkaloid poisoning can occur after consumption of any medicinal plant from Solanaceae family as contaminants. Globally, almost all reports from 1978 to 2014 include one

of the herbs prescribed in herbal teas. Contamination is most likely to occur during harvesting or processing. For herbs, on-site inspection is required to exclude cross-contamination at the retail level and accidental mixing. The diagnosis is confirmed by screening for the presence of Solanaceae species and tropane alkaloids. Since, if these relatively heat-resistant alkaloids contaminate the herbal teas and other herbs in large quantities, significant health hazards may occur, the significance of good agricultural and collection practices (GACPs) for medicinal plants is accentuated by WHO repeatedly. The DNA barcode is also increasingly used to exclude the presence of pollutant (especially toxic species) and product substitution. All suspect cases should be reported to health authorities so that investigations throughout the supply chain and early intervention measures to protect the public can be taken [7].

4. Herb-drug interactions with the plants including furanocoumarins

Naturally occurring furanocoumarins are abundant in citrus fruits, vegetables, and medicinal herbs from the Apiaceae, Fabaceae, and Rutaceae families. Grapefruit-drug interactions were first discovered by chance in 1989 where 5-fold higher felodipine plasma concentrations were observed. Consumption of grapefruit juice has increased the oral bioavailability of various drugs, including calcium channel blockers (e.g., felodipine, nifedipine), HMG-CoA reductase inhibitors (simvastatin, lovastatin), benzodiazepines (midazolam, triazolam), antihistamines (terfenadines), and immunosuppressants (cyclosporine). In addition, phototoxicity developing with furanocoumarins occurs as a result of exposure to sunlight, following contact with the plant. Phototoxicity results in acute dermatitis, sometimes blisters, and vesicles. In many cases, prolonged hyperpigmentation is observed. Photochemotherapy for a long time with furanocoumarins can also cause cancer (skin and liver) [8].

5. Toxicity of pyrrolizidine alkaloids

Pyrrolizidine alkaloids (PAs) are common components of hundreds of plant species of unrelated botanical families scattered across many geographical regions of the world. In more than 6000 plants belonging to three large plant families, Asteraceae, Boraginaceae, and Fabaceae, above 660 PAs and PA *N-oxides* have been identified and about half of them are toxic. More than 10,000 cases of PAs poisoning have been documented worldwide, most of which resulted from exposure to food contaminated with PAs. Acute toxicity from PA is mainly seen in the liver, including hemorrhagic necrosis, hepatic megalocytosis, venous occlusion, liver cirrhosis, and hepatic carcinomas, and chronic exposure to PAs, from herbs/dietary products containing PAs, can lead to kidneys, pancreas, gastrointestinal tract, bone marrow, and brain. It is a worldwide public health problem due to the high risk of human exposure to genotoxic and tumorigenic PAs, and the International Program on Chemical Safety has concluded that PAs are a threat to human health and safety. Regulations have been constituted to restrict its use [8].

6. Adverse effects of anthraquinone derivatives

Anthraquinone derivatives with a laxative effect appear in a number of plants: *Sennae folium*, rhei rhizoma, frangulae cortex, and aloe. They have a laxative effect by directly stimulating the colonic smooth muscles. The adverse effects of laxative anthraquinone drugs are more likely to be caused by excessive loss of

fluids and electrolytes, especially potassium loss, associated with the use of high doses. Higher doses also drain a larger portion of the colon, and the resulting natural absence of defecation over the next day leads to reuse of anthraquinone. Prolonged use of laxatives due to laxative addiction should be avoided, as it may have a detrimental effect on the intestinal mucosa, leading to a condition known as Melanosis coli. This is usually seen after at least 9–12 months of regular stimulant laxative use. Undesirable effects such as abdominal spasms and pain, urine color change by metabolites, and hemorrhoid congestion are common. A report from China reported that patients with senna leaf tea addiction as laxatives suffer from symptoms of fidgetiness, sleeplessness, dilated pupils, and loss of appetite while consuming 5–9 g of senna daily. Rare cases of hepatic inflammation induced by anthraquinone derivatives have been reported and may be dose dependent. Hypokalemia, which occurs as the effect of long-term use of laxative drugs, strengthens the effect of cardiac glycosides and interacts with antiarrhythmic drugs. Using other drugs (diuretics, adrenocorticosteroids, and licorice) that cause hypokalemia can speed up electrolyte imbalance. Contraindications for anthracene laxatives are intestinal obstruction and chronic intestinal inflammation such as stomach or duodenal ulcer or ulcerative colitis [9].

7. Adulterations

Many reports on the adulteration of herbal products with synthetic drugs have been systematically reviewed and published with case reports. The list of herbal products and adulterants produced in this way is quite impressive and caused serious side effects (**Table 3**). A case with the latest herbal product adulterated is related to a 56-year-old man from Indonesia. While visiting Australia, he was hospitalized in a mixed condition arising from hypoglycemia. He insisted that type II diabetes was controlled only by diet. However, despite dextrose infusions, glucose levels do not normalize. It was eventually discovered that he also received a TCM "Zhen Qi" from Malaysia. It was analyzed and shown to contain glibenclamide. Like that, in some cases, patients were severely damaged. Examples of serious side effects include agranulocytosis, Cushing's syndrome, coma, over-anticoagulation, gastrointestinal bleeding, arrhythmias, and various skin lesions. Due to the adulteration of herbal products with synthetic drugs, adequate and necessary procedures should be applied, and whole herbal products should be analyzed before marketing [10].

Acetaminophen	**Dexamethasone**	**Glibenclamide**
Aminopyrine	Dexamethasone acetate	Hydrochlorothiazide
Betamethasone	Diazepam	Hydrocortisone
Caffeine	Diclofenac	Indomethacin
Chlordiazepoxide	Ethoxybenzamide	Mefenamic acid
Chlorzoxazone	Fluocinolone acetonide	Methylsalicylate
Clobetasol propionate	Fluocortolone	Phenacetin
Corticosteroids	Fluocortolone	Phenylbutazone
Phenytoin	Prednisolone	Sibutramin
Sildenafil		

Table 3.
Adulterants found in herbal products.

8. Heavy metal contaminations

It is possible to come across heavy metals such as cadmium, cobalt, copper, iron, manganese, nickel, lead, zinc, and mercury in concentrations that are not produced within the framework of certain rules, especially the traditional Chinese herbal preparations. This contamination is probably caused by contamination during drying and preservation. With severe complications that may occur, these types of products are unlikely to cause adverse health effects, even if they are not consumed in large quantities for long periods of time [11].

9. Herb-drug interactions (HDI)

There are no molecules in nature that have no effect. Therefore, this diversity increases the variety of products while increasing the probability of interaction. If the effect of a drug is changed qualitatively or quantitatively by another substance (herbal medicine/product/ingredient), there is an interaction between these two drugs. It can be said as a rule that two drugs should be present at the same time in the body, especially in the place of interaction, for interaction to occur. But sometimes, if the drug causes a permanent effect on the body, interaction can occur even if such a drug is not found in the body. Interaction is sometimes deliberately created to increase the therapeutic effect of one drug with another drug or to reduce its side effects, which are useful interactions. In other cases, the interaction may occur undesirably as a result of unauthorized use of medicines or when the patient is starting treatment with a particular medication. Sometimes, unpredictable interactions due to new drugs may occur. Drug-related as well as disease-related factors (patient's age, gender, genetic characteristics, pathological condition), such as the posology and method of administration, pharmacokinetic, pharmacodynamic, and therapeutic properties of the drug may cause interactions between medicines and herbal medicines (**Figure 1**) [12].

It is observed that the use of herbal medicines/herbal products is more common in the geriatric group aged 65 and over, and the use in women in this adult population is higher than in men. Herbs/herbal products/drug interaction is higher in patients using drugs with narrow therapeutic index. Information on herbs-herbal products/drug/component interactions is based on *in vitro* tests, *in vivo* animal experiments,

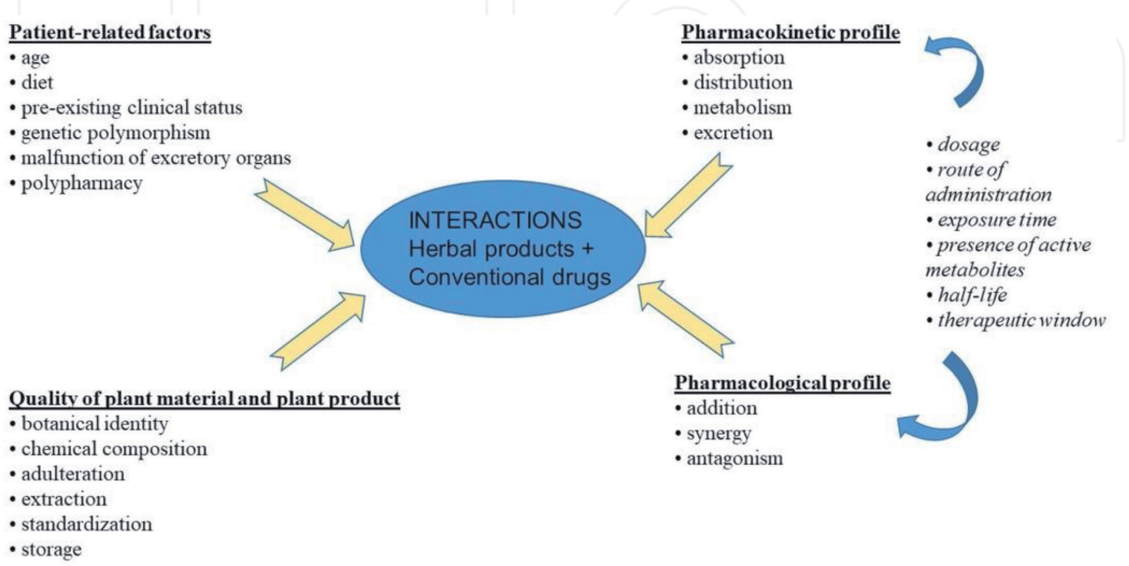

Figure 1.
The important risk factors that influence the occurrence of interactions between herbal products and conventional drugs [13].

and case reports. Many mechanisms play a role in these interactions, and interactions are seen in two main types as pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions result in changes in drug absorption, distribution, metabolism, and elimination. These interactions usually occur far away from the drug's effect and lead to a decrease or increase in effect as a result of the change in drug concentration in body fluids. In order to say that there is a pharmacokinetic interaction, the plasma level or half-life of the drug should be determined experimentally. Various interactions such as cytochrome P450, UDP-glucuronyl-transferase (UGTs), and carrier proteins such as P-glycoprotein (P-gp) are thought to play a role in these interactions. Pharmacokinetic interactions are the most common interactions as a cause of undesirable side effects. If the herb or natural products or its secondary metabolites inhibit an enzyme involved in drug metabolism, it may increase the potential for toxic effects, as it will reduce the metabolism of drugs that metabolize the enzyme and turn into an inactive metabolite as a result of metabolism. If the herbal drug induces an enzyme, a decrease in drug effect may be observed, since the metabolism of the drugs that are metabolized by this enzyme and converted into inactive metabolite as a result of metabolism will increase. Likewise, if the drug turns into an active metabolite as a result of metabolism, if the herbal drug induces the enzyme responsible for the metabolism of the drug, an increase in drug effect or toxic effect may be observed as a result of increased effective metabolite concentration [12].

Pharmacodynamic interactions occur when one drug changes the effect of another, that is, an effect opposite or in the same direction, chemically combined with it. That is, if the herbal medicine and drug affect the same receptor or the same site, interaction occurs and a synergic or antagonistic effect may occur. While the effect of the drug increases as a result of the additive effect, the effect of the drug decreases or disappears as a result of the antagonistic effect. The concentration of the drug in body fluids, plasma, is not changed by the second drug. Although most of the drug metabolism is carried out in the liver with cytochrome P450 enzymes, the metabolism of some drugs can be in the blood, kidney, skin, and intestine. Approximately 50 different cytochrome P450 enzymes have been identified. However, a small portion of these enzymes play a role in drug metabolism. Herbal drug-drug interactions are generally pharmacokinetic-type interactions that result from enzyme inhibition or induction [12].

The following are the evaluation parameters used to determine the probability of herb-drug interactions:

a. Adequate patient history.

b. Concurrent diseases, conditions, or other drugs associated with adverse events.

c. Concomitant medications are documented.

d. The description of the interactors is sufficient.

e. Clearly, alternative explanations are excluded.

f. Chronology is complete.

g. The time sequence of drug administration to adverse event is reasonable.

h. An adverse event has been sufficiently defined.

i. The event ends after stopping the medicine.

j. The activity repeats upon challenge again [3].

9.1. Herb-drug interactions in the treatment of cardiovascular disorders (CVDs)

In 2015, an estimated 422.7 million cases of cardiovascular disease (CVD) and 17.92 million CVD deaths were reported worldwide. And most people in the world still prefer complementary and alternative medicine (CAM) as their first treatment option. The consumption of over-the-counter CAM consumption increases the risk of HDI, which endangers the effective medical management of CVD. In cardiac therapy, the narrow therapeutic drug window and a wide range of cardiac drugs available for treatment are also a major cause of concern for HDI. People with chronic diseases often use CAM therapies inappropriately to manage their condition and thereby increase the potential or possibility of HDI formation [1].

This section of our review focuses on plants reported in the literature by preclinical or clinical studies (rats or humans) or cardiovascular drugs with appropriate case reports. These herbs are reported to affect the pharmacokinetics of some cardiovascular drugs through a variety of HDI mechanisms. Reported HDI studies of some plants commonly used for the treatment of CVDs are summarized in **Table 4** [1].

Herbs	Interacting drugs	CYP, P-gp induction/inhibition
Piper longum L.	Verapamil, digoxin, propranolol	CYP3A4, CYP2D6 and CYP1A2 (inhibition)
Curcuma longa L.	Losartan, rosuvastatin, warfarin, clopidogrel	CYP3A4, CYP1A2, CYP2B6, CYP2C19, CYP2C9 (inhibition)
	Talinolol	P-gp induction, intestinal P-gp in subjects with ABCB1 C3435T genotype inhibition
Fucus vesiculosus L.	Amiodarone, valsartan	CYP1A (induction), CYP2C9 (inhibition)
Zingiber officinale Roscoe	Nifedipine, phenprocoumon	CYP2C9 (potent inhibition) CYP2C19, CYP3A4 (moderate inhibition)
Terminalia bellirica (Gaertn.) Roxb.	Diltiazem	CYP3A4 CYP2D6
Salvia miltiorrhiza Bunge	Warfarin	CYP3A4 (induction) CYP1A2, CYP2C9, CYP1E1, CYP2C6, CYP2C11 (inhibition)
Allium sativum	Atorvastatin, cilostazol	CYP2C9, CYP3A4 and CYP2D6 (inhibition) P-gp induction
Ginkgo biloba	Diltiazem, cilostazol	CYP1A2, CYP3A, and CYP2C9 (P-gp inhibition inhibition) CYP2C19 (induction)
	Nifedipine	Unknown
	Talinolol	Intestinal P-gp inhibition
Glycrrhiza glabra	Atorvastatin, simvastatin, lovastatin	CYP2B6, CYP2C9, CYP2C19 (inhibition) CYP3A4 (induction)
Panax ginseng	Warfarin	CYP3A4 (induction), CYP2C11 (inhibition)
	Nifedipine	CYP3A4 (inhibition)
Pueraria montana (Lour.) Merr. var. *lobata* (Willd.) Sanjappa & Pradeep	Warfarin	CYP 1A2 (induction) CYP2D6, CYP3A4, and OATs (inhibition)
Citrus paradisi Macfad.	Felodipine	CYP3A4 (inhibition)
	Talinolol	OATP inhibition
	Aliskiren	OATP2B1 inhibition
	Atorvastatin	Intestinal CYP3A4 inhibition
	Lovastatin	Intestinal CYP3A4 inhibition
	Simvastatin	Intestinal CYP3A4 inhibition

Herbs	Interacting drugs	CYP, P-gp induction/inhibition
Mentha × piperita L.	Felodipine	CYP3A4 (inhibition)
Hypericum perforatum	Nifedipine	CYP3A4 (induction)
	Verapamil	
	Digoxin	P-gp induction
	Talinolol	P-gp induction
	Phenprocoumon	CYP2C9 induction, CYY3A4 induction
	Atorvastatin	CYP3A4 induction, P-gp induction
	Pravastatin	Intestinal CYP3A4 inhibition
	Simvastatin	CYP3A4 induction, P-gp induction
	Rosuvastatin	P-gp induction
Camellia sinensis (L.) Kuntze.	Digoxin	P-gp induction, digoxin uptake inhibition
	Nadolol	Intestinal OATP1A2 inhibition
	Rosuvastatin	Intestinal OATP1A2/OATB2P inhibition
Malus pumila Mill.	Atenolol	Unknown (possible mediated by OATP function and modulation of intestinal drug uptake)
	Aliskiren	OATP2B1 inhibition
Schisandra chinensis (Turcz.) Baill.	Talinolol	P-gp inhibition
Citrus × sinensis (L.) Osbeck	Aliskiren	OATP2B1 inhibition
Silybum marianum (L.) Gaertn.	Losartan	CYP2C9 inhibition

Table 4.
Reported HDI studies of some commonly used herbs for the treatment of CVDs [1, 13].

9.2 Herb-drug interactions with chemotherapeutic drugs

One of the most important risks associated with the combined use of herbal products and chemotherapeutic agents is herb-drug interactions. Patients with chronic illnesses who use more than one drug have a higher risk. Herb-drug interaction is undesirable in the treatment of cancer due to the perpendicular dose-effect relationship and toxicity of chemotherapeutic agents. The most common mechanism of herb-drug interaction is herbal mediated inhibition and/or stimulation of drug-metabolizing enzymes and/or transport proteins that lead to changes in the pharmacokinetic order of the victim drug. This focus on clinically significant herb-drug interaction should attract public attention, including practitioners, researchers, and cancer chemotherapy consumers (**Table 5**) [14].

9.3 Herb-drug interactions with attention-deficit/hyperactivity disorder (ADHD) medication

In some pediatric patients with attention deficit/hyperactivity disorder (ADHD), natural products such as herbal medicines are used. Although herbal remedies are thought to be safe when used appropriately, they may contain active ingredients that can interact with concurrently used medications and can lead to adverse events for natural products-drug interactions (**Table 6**) [15].

Herbs	Cancer drugs	Study type	Results
Echinacea	Etoposide	Case report	It was found that taking echinacea with etoposide rarely reduced platelet (16 × 103/L) compared to etoposide alone (44 × 103/L)
	Docetaxel	Prospective study in 10 cancer patients	Echinacea did not cause a significant change in the pharmacokinetics of docetaxel
Garlic	Docetaxel	Prospective, patient controlled, pharmacokinetic	Garlic was found to reduce docetaxel clearance. Although this reduction is not statistically significant, it can potentially increase side effects due to docetaxel accumulation
Ginseng	Imatinib	Case report	After receiving ginseng in patients receiving imatinib for 7 years, hepatotoxicity symptoms began to appear. Hepatotoxicity improved upon discontinuation of ginseng
Grapefruit juice	Docetaxel	Case report	Grapefruit juice has been found to reduce the clearance of docetaxel, while increasing the AUC and terminal half-life of docetaxel
	Nilotinib	Open label, randomized, 2 period crossover	It was found that grapefruit juice increased the AUC and the peak concentration of nilotinib, but did not affect the elimination half-life
Milk thistle	Irinotecan	Pharmacokinetic study	It has been found that milk thistle causes a statistically insignificant decrease in irinotecan clearance, which is unlikely to cause a clinical effect
St John's wort	Docetaxel	Pharmacokinetic study	St John's wort was found to cause a significant decrease in plasma docetaxel concentration
	Irinotecan	Unblinded, randomized crossover study	St John's wort caused a 42% reduction in plasma concentrations of the active metabolite (SN-38)
	Imatinib	Open-label, crossover pharmacokinetic study	St John's wort reduced the plasma concentration of imatinib by 32% and reduced the half-life of imatinib by 21%
		2-period, open-label, fixed sequence study	St John's wort increased the imatinib clearance by 43% and decreased the plasma concentration by 30%

Table 5.
Herbal interaction studies with chemotherapeutic agents conducted in human subjects [14].

9.4 Herb-drug interactions (HDI) with chronic kidney disease (CKD) medication

Chronic kidney disease (CKD) is defined as abnormalities in kidney structure or function that have been going on for more than 3 months, with adverse health consequences. The prevalence of CKD is estimated to be 8–16% worldwide.

Herbs	Drugs	Case
Ginkgo biloba	Strattera	An 8-year-old male patient with a history of ADHD, astigmatism, behavioral disorder, learning disorder, and asthma was using 25 mg Strattera for ADHD from October 2008 to September 2009. From May 2001 to November 2010, he was taking 85 mg of *G. biloba* daily. After starting Strattera, the patient experienced headaches and eye pain resulting in hospitalization. On ophthalmological examination, suspicion of glaucoma appeared. The reporting child psychiatrist stated that the incident was related to Strattera
Efalex evening primrose oil	Ritalin	A 7-year-old female was treated with Ritalin 10 mg/day orally for ADHD from October 2001. The patient has also been taking Efalex evening primrose oil since 2001. On March 7, 2002, she developed a tic including her both arms. It has become more complex. Ritalin was discontinued on March 7, 2002. There was an improvement in head, arm, neck, and leg movements after cessation, but movements were still present. There was no history of tic or movement disorders in the family. Before the tics, the patient had a nightmare for 1 week. She also had a skin rash and dry skin in her mouth. The case was considered medically significant
Evening primrose oil	Concerta	An 11-year-old male was using 36 mg of methylphenidate per day for ADHD for several years. The patient was also taking evening primrose oil for an unknown indication and duration. There was a history of moderate to severe developmental delay and slow learning. Methylphenidate was exhausted on December 30, 2002 and was brought to emergency with severe torticollis, rolling arm movements, lip chewing, and pharyngitis. On January 2, 2003, he presented to the pediatrician with the same symptoms and speech disorder, did not eat or drink, and was hospitalized. Torticollis improved with intravenous cetirizine hydrochloride. The patient was also diagnosed with pharyngeal abscess
St John's wort	Concerta	A 17-year-old female with a history of ADHD and depression was treated with methylphenidate for about a year. Concurrent medication included St. John's wort. The patient experienced psychotic symptoms on an unknown day. The patient saw and heard things that were not there and disturbed at night. The result was considered medically significant
	Ritalin	A 15-year-old male started 20 mg oral/day Ritalin for ADHD in 1998 and tolerated it well. He suffered a period of sadness from June 1, 2001, and he took St. John's wort (five drops) orally to treat his depression. A few hours later he presented agitation, unexplained crying, depression-changing aggression, and difficulty concentrating. On June 6, 2001, St. John's wort ceased and these symptoms subsided. Three weeks later, St. John's wort was restarted and the same symptoms appeared. St John's wort was quitted and symptoms were relieved again. The reaction was considered medically significant

Table 6.
Description of adverse status reports evaluated for the cause of natural product-drug interactions [15].

Most importantly, patients with CKD are advised to avoid over-the-counter products and herbal medicines according to the Kidney Disease Improving Global Outcome (KDIGO) guidelines. However, several studies have revealed that many patients with CKD have returned to complementary and alternative medicine (CAM) for a desperate treatment. The consumption of unregistered herbal products is more common today because these products can be easily purchased from on-line media, street markets, or stores. It is an alarming trend as it may be linked to an increase in the number of patients with liver and kidney failure in public hospitals. In addition, patients with CKD are at higher risk of developing cardiovascular disease. Most of them are prescribed with antiplatelet and anticoagulants. Anti-platelets and anticoagulants

may interact with synergistic or additives with CAM products, which can cause blood-thinning effects that may later cause excessive bleeding (**Table 7**) [16].

Herbs	**Dosage form/doses associated with safety concerns**	**Safety concerns**
Panax ginseng	Crude and standardized *Ginseng* root extract, high doses, combined preparation	It may hypoglycemic effect and can cause hypertension, as well as may interact with anticoagulants
Ginkgo biloba	Standardized *Ginkgo* extract (EGb 761, 80 mg/day), crude *Ginkgo* plant parts (5 ppm of toxic ginkgolic acid)	It may interact with anticoagulants and can cause a severe allergic reaction
Cinnamomum cassia (L.) J.Presl	Cinnamon extract	It may have hypoglycemic effect and may cause worsen liver conditions
Zingiber officinale	Dried root, liquid extract, doses >10 g/day	It may interact with anticoagulants
Allium sativum	Fresh garlic, dried powder (>7 g/day), higher doses than usual dietary intake	It may interact with anticoagulants, antihypertensive, anti-hyperlipidemic, and hydrochlorothiazide
Andrographis paniculata (Burm.f.) Nees	*Andrographis paniculata* extract (50 and 100 mg/kg/day) for 14 days, standardized *Andrographis* extract	It may interact with hepatic metabolizing enzymes, anticoagulant, antiplatelet, anti-hyperglycemic, barbiturates
Momordica charantia L.	Bitter melon tea, bitter melon extract administered intravenously and intraperitoneally, high-dose bitter melon seed	It may hypoglycemic effect and may interact with hypoglycemic agents, death in children
Punica granatum L.	Pomegranate juice, pomegranate extract	It may possibly interact with anticoagulants
Angelica sinensis (Oliv.) Diels	Dong Quai extract (tablet), dose: 565 mg (1–2 tab/day) for 4 weeks	It may increase the risk of bleeding, increase cancer risk, as well as may interact with anticoagulants, antiplatelet, estrogen (augments the effect of estrogen)
Medicago sativa L.	Alfalfa seed products	It may cause autoimmune diseases (SLE, multiple sclerosis, rheumatoid arthritis), photosensitivity, estrogen-like and hypoglycemic effects, and may interact with immunosuppressants, warfarin, oral contraceptives, estrogen conjugates, oral hypoglycemic agents, iron, vitamin
Trigonella foenum-graecum L.	Fenugreek seeds, fenugreek seed powder (>5 g)	It may have a hypoglycemic and estrogen-like effects
Camellia sinensis	Tea (high dose >600 mg/day or 2.25–4.5 L/day)	It may cause liver problems, and may interact with nadolol (beta-blocker), diuretics
Morinda citrifolia L.	Noni juice, dose >400 mL	It may cause liver toxicity, and contains high potassium
Spirulina	A product containing blue-green algae	It may increase the risk of bleeding, may interact with immunosuppressant, antiplatelet, anticoagulants, NSAIDs, other herbs that reduce blood clotting (e.g., ginseng, garlic, ginkgo)

Table 7.
The herbs used by CKD patients and their safety concerns [16].

9.5 Herb-drug interactions with menopause medication

Herbal remedies are popular among women to relieve menopausal symptoms such as hot flashes, energy loss, depression, joint pain, and insomnia. As recently reviewed, a variety of herbs used to treat menopausal symptoms can cause herb-drug interactions (**Table 8**) [17].

Herbs	HID
Cimicifuga racemosa	Increase the activity of antihypertensive agents
Angelica sinensis	Inhibit platelet aggregation and increase risk of bleeding if co-medicated with anticoagulants
Oenothera biennis L.	Potentially interacts with anti-inflammatory drugs, corticosteroids, beta-blockers, antipsychotics and anticoagulants
Trifolium pratense L.	Increase the activity of CYP3A4 and alters the metabolism of drugs
Humulus lupulus L.	Interact with CNS depressants, antipsychotics, hormones and CYP-metabolized drugs

Table 8.
Herb-drug interactions with herbs for menopause.

10. Herb-micronutrient interactions

The ability of some foods to reduce or increase the absorption of various vitamins and minerals has been known for years. Almost half of the population regularly uses some herbal products as a dietary supplement, along with the vitamin and mineral supplements. The use of these products has increased significantly over the past two decades, and a number of clinically relevant herbal drug interactions have been identified during this time. Therefore, it is likely that the mechanisms underlying many herb-drug interactions may also affect micronutrient absorption, distribution, metabolism, and excretion. Not taking these eccentricities into account can negatively affect the outcome and interpretation of any advanced herb-micronutrient interaction studies [18] (**Table 9**).

Phytochemicals	Micronutrient affected	Effect and interaction mechanisms
Plant polyphenols (PPs) (tea catechins, phloretin, quercetin)	Iron	PPs reduce absorption through complexation
	Folate, ascorbate	PPs reduce absorption through uptake transporter inhibition
Silymarins	Iron	They reduce absorption through complexation
Phytic acid	Calcium, iron, zinc	It reduces absorption through complexation
Hyperforin (St. John's wort)	Vitamin D3	It enhances plasma clearance through induction of CYP3A4 metabolism

Table 9.
Herb-micronutrient interactions and their mechanisms.

11. Databases setup for plants/dietary supplements

The Integrative Medicine Service at Memorial Sloan Kettering Cancer Center has developed About Herbs (www.aboutherbs.com), which provides research information, including alleged uses, side effects, and herb-drug interactions for about 284 dietary supplements. Using Google Analytics, they have detected that more than 26,317,000 hits have been recorded since November 2002. According to these data, top 10 plant and/or dietary supplements in 2018 were chaga mushrooms, turmeric, ashwagandha, reishi mushroom, graviola, Active Hexose-Correlated Compound, boswellia, dandelion, green tea, and *Coriolus versicolor*. In **Table 10**, based on the literature researches in PubMed, their scientific and common names, plant-drug interactions and their appropriate use in the oncology environment are discussed. In the past 16 years, evidence of the use of these supplements is based on limited studies and mostly preclinical findings. It is important to inform healthcare professionals about popular dietary supplements so that patients can be informed to make decisions that maximize benefits and minimize risks [19] Hereby, important herb-drug interactions have been compiled in **Table 11**.

Common name	Scientific name of the plants/dietary supplements	Key interaction and concerns	Avoid in
Chaga	*Inonotus obliquus* (Ach. ex Pers.) Pilát	High in oxalates Anticoagulants Anti-platelets Antihyperglycemic agents	Renal disease Diabetic patients on treatment (acarbose)
Turmeric	*Curcuma longa*	High in oxalates CYP2C9 enzyme	Renal disease
Ashwagandha	*Withania somnifera* (L.) Dunal	Increase testosterone levels in men	Prostate cancer
Reishi mushroom	*Ganoderma lucidum* (Curtis) P.Karst.	Anticoagulants Anti-platelets	Radiation therapy
Graviola	*Annona muricate* L.	Antihyperglycemic agents	Diabetic patients on treatment
AHCC	*Active Hexose-Correlated Compound*	CYP2D6 enzyme inducer	Breast cancer patients on doxorubicin, zofran, and aromatase inhibitor (letrozole)
Boswellia	*Boswellia serrata* Roxb. ex Colebr.	Unknown	Contact dermatitis
Dandelion	*Taraxacum mongolicum* Hand.-Mazz., *T. officinale* (L.) Weber ex F.H.Wigg	CYP1A2 enzyme Diuretic Antihyperglycemic agents Estrogenic activity	Hormone-sensitive breast cancer
Green tea	*Camellia sinensis*	High doses or taken on an empty stomach can cause liver toxicity Bortezomib	Elevated liver function tests
Turkey tail mushroom	*Trametes versicolor* (L.) Lloyd	Unknown	Patients on immunosuppressants (in theory)

Table 10.
Top 10 monographs accessed from the "about herbs" database in 2018.

Plants	Effect and usage	Drugs	Interactions
Allium sativum	Antihypertensive, antithrombotic, fibrinolytic, antimicrobial, antidiabetic and lipid-lowering properties [20]	Anticoagulant	May lead to increased anticoagulation effect of warfarin and may increase the risk of bleeding [21–23]
		Antiretroviral (saquinavir)	May decrease the plasma level of protease inhibitor saquinavir [24, 25]
		Antidiabetic (metformin, chlorpropamide)	May occur greater reduction in blood glucose level [26, 27]
		Paracetamol (acetaminophen)	May change some pharmacokinetic variables of paracetamol [28]
Aloe vera L.	Laxative antidiabetic [20]	Corticosteroids and potassium-depleting diuretics	Laxative and potassium lowering effect may result in hypokalemia [29, 30]
		Cardiac glycosides and antiarrhythmic drugs	May enhance the hypokalemia-related arrhythmia [29, 30]
		Antidiabetics	Because of the glucose-lowering effects, diabetic patients should be careful when combining with an antidiabetic agent [31]
Cassia senna L.	Laxative [20]	Corticosteroids and potassium-depleting diuretics	May lead to hypokalemia, since senna can cause excessive water and potassium loss, theoretically [20]
		Digitalis glycosides	Risk of digitalis toxicity due to hypokalemic effect of senna, theoretically [20]
Echinacea purpurea (L.) Moench.	As immunostimulant and in treatment of upper respiratory tract infections [20]	Anabolic steroids, amiodarone (antiaritmic), methotrexate (chemotherapy agent-immunosuppressant), ketoconazole (antifungal), and acetaminophen	The risk of hepatoxicity by concomitant usage of potentially hepatoxic *Echinacea* [32, 33]
		Immunosuppressants	Might decrease the effects of immunosuppressants, theoretically [34]
		Midazolam (benzodiazepine)	May increase oral bioavailability of midazolam or [20]

Plants	Effect and usage	Drugs	Interactions
Ginkgo biloba	To improve cognitive functions, cerebrovascular disorders and vertigo [20]	Phenobarbital	Reduces the therapeutic potency of phenobarbital [35]
		Ibuprofen (NSAID)	May cause fatal intracerebral bleeding [36]
		Anticoagulant (warfarin) and antiplatelet (aspirin) drugs	Possible additive inhibition on platelet aggregation [37, 38]
		Antidepressant (trazodone)	*Ginkgo* flavonoids increase the production of 1-(m-chlorophenyl) piperazine (mCPP), an active metabolite of trazodone. Flavonoids and mCPP may induce the enhancement of GABAergic activity [34]
		Thiazide diuretic (not specified in the original paper)	Further increase in blood pressure [39]
		Nicardipine (a calcium channel blocker)	Decreasing the hypotensive activity of drugs [40]
		Nifedipine, diltiazem (calcium channel blockers) and talinolol (β-blocker)	Possible increased antihypertensive activity resulting from high bioavailability [41–44]
		Cyclosporine	Decreased bioavailability of drug [45]
		Midazolam (benzodiazepine)	Decreased bioavailability of drug [46]
		Propranolol (β-blocker)	Decreased the plasma concentrations of propranolol [47]
		Theophylline	Less efficacy with *Ginkgo* [48]
		Omeprazole (proton pump inhibitor)	May induce the metabolism, and reduce the effect of omeprazole [49]
		Tolbutamide (an antidiabetic drug)	May increase or decrease the hypoglycemic effect of tolbutamide [50]
		Amikacin (aminoglycoside)	Amikacin ototoxicity may enhance [51]
Glycyrrhiza glabra	Expectorant, antispasmodic and anti-inflammatory properties and in treatment of peptic and duodenal ulcers [20]	Prednisolone (corticosteroid)	Glycyrrhizin increases the plasma concentrations and potentiates pharmacological effects of prednisolone [52, 53]
		Hydrocortisone (corticosteroid)	Glycyrrhetinic acid potentiates the activity the topical cutaneous vasoconstrictor effect [54]
		Dexamethasone (corticosteroid)	Dexamethasone induces the mineralocorticoid effects of glycyrrhizin [55]
		Antihypertensives	Mineralocorticoid effects (sodium and water retention and hypokalemia) of plant reduce the efficacy of the drugs that use to lower blood pressure. Hypokalemic effect of the plant may increase the effect of the loop and thiazide diuretics [20]

Plants	Effect and usage	Drugs	Interactions
Hypericum perforatum	To treat depression, seasonal affective disorder, anxiety and insomnia, especially related to menopause [20]	Gliclazide (an antidiabetic drug)	Increases the apparent clearance of gliclazide [56]
		Carbamazepine, phenytoin and phenobarbital (antiepileptics)	Clinically significant interaction is unlikely, but *Hypericum* should be used carefully with these antiepileptic drugs [20]
		Alprazolam, midazolam, triazolam and quazepam (benzodiazepines)	Since the main compound hyperforin induces the enzyme CYP3A4, bioavailability may decrease [20, 57]
		Indinavir (protease inhibitor) Nevirapine (nonnucleoside reverse transcriptase)	May decrease the antiretroviral drugs and may lead to development of drug resistance [58, 59]
		Cyclosporine, tacrolimus, (Immunosuppressants)	May decrease the blood levels and may lead the acute organ rejection in transplant patients [60–62]
		Warfarin and phenprocoumon (anticoagulants)	May cause a moderate reduction in the anticoagulant effects of the drugs [20]
		Simvastatin and atorvastatin (antihyperlipidemic agents)	May observe the increasing serum level of total cholesterol [63, 64]
		Nifedipine, verapamil (calcium channel blockers) and talinolol (a β-adrenoceptor blocker)	May decrease the bioavailability of drugs [65]
		Oral contraceptives	Associated with increased metabolism of ethinyl estradiol, norethindrone, and ketodesogestrel, and may cause bleeding and unwanted pregnancy [66–69]
		Carbamazepine (antiepileptic)	Should be considered a mild interaction between carbamazepine and *Hypericum*
		Sertraline, nefazodone (selective serotonin reuptake inhibitors)	May be occurred the symptoms of central serotonergic syndrome [70]
Linum usitatissimum L.	Demulcent for bronchitis and coughs, and topically used for burns [20]	Anticoagulant or antiplatelet drugs	In the view of the thought that omega-3 fatty acids such as linolenic acid have antiplatelet effects, should be concerned about the possibility of prolonged bleeding [20]

Plants	Effect and usage	Drugs	Interactions
Panax ginseng	Adaptogenic [20]	Phenelzine (MAO inhibitor)	Additive nervous system effect of drug such as headache, tremor, sleeplessness and mania [34]
		Warfarin (anticoagulant)	INR may decrease by concomitant usage [71]
		Warfarin, heparin, aspirin, and NSAIDs	There is no clear data, but due to the antiplatelet components in *P. ginseng*, it should be avoided concomitant using [32]
		Caffeine	Possible additive stimulant effects [20]
Piper methysticum	Anxiolytic, sedative, aphrodisiac	Barbiturates and benzodiazepines	Might potentiate the effects of central nervous system depressants [72]
		Alprazolam (benzodiazepine)	Risk of coma due to possible additive effect on GABA receptor [72]
		Levodopa	May reduce the efficacy due to possible dopaminergic antagonism [73]
		Acetaminophen	May enhance the risk of hepatotoxicity [33]
Valeriana officinalis	Used for stress and insomnia as sedative and anxiolytic [20]	Barbiturates	Excessive sedation. The active component valerenic acid seems to likely to have the additive effect to phenobarbital [74]
		Other central nervous system depressants such as benzodiazepines and opioids	Possible additive sedative effects [20]
		Caffeine	Possible reverse effect to the sedative effect of Valerian [20]
Zingiber officinale	To reduce nausea and emesis induced by pregnancy, chemotherapy, and postoperative ileus [75]	NSAIDs	May reduce the platelet aggregation and enhance the bleeding tendency [33]
		Nifedipine	May potentiate the antiplatelet effects [76]
		Metronidazole	May increase the bioavailability [77]
		Glibenclamide (antidiabetic)	May reduce the blood glucose level [26]

Table 11.
Some herb-drug interactions.

12. Criteria for risk assessment of herbal products

There have been an increasing number of herbal products as food ingredients or supplements, which are a commercially important part of the health food market. Herbal products can range from whole foods (e.g., cranberry against urinary infections) to pharmaceutical-like preparations in unit dose form, such as tablets, capsules, or drops, and are thought to provide additional benefits beyond basic nutrition. The regulatory position on food supplements is uncertain (food or medicine?), and there is concern about the safety assurance of these products. Several cases of poisoning have been reported with herbal products. In some cases, these were caused by contamination with other plant species, but this is not always the case. In addition, toxic components (e.g., pyrrolizidine alkaloids) are accumulated at different concentrations in different parts of the source plant, and climatic and agronomic differences lead to great variability in the composition [78].

Therefore, it is not possible to provide a simple checklist of suitable tests to ensure the safety of herbal products. International guidelines are available for the safety assessment of herbal product and should be designed to cover all life stages to ensure a lifelong intake that can be consumed without significant health risk [78].

Information relating to herbal product identification, characterization, and standardization:

A. Botanical source: identity to family (geographic origin), genus, and species of source plant (with authority), and, if relevant, variety and chemotype; common names as well as part(s) of plant used. Evidence from previous human exposure through food or other sources (ethnobotanical and folk medicine studies).

B. Growing conditions: wild or cultivated plant (Good Agricultural Practice—GAP), site and time of harvest; stage of growth at harvest, post-harvest treatment (drying, fermentation, etc.), storage conditions, phytosanitary measures pre- and postharvest (including use of and limits for pesticides) are very important.

C. Raw material (fresh or dried plant materials): specifications according to standard reference (e.g., herbal Pharmacopoeias), identity tests (macroscopic, microscopic, FT-IR, TLC, GC, HPLC, etc.), quantitative tests (especially constituents related for efficacy and/or toxicity).

D. Process applied to starting material: preparation steps (e.g., separation, extraction processes, solvents), methods used, handling specific precautions; e.g., light/temperature sensitivity, oxidation, etc.

E. Botanical preparation: standardization criteria (markers: active constituents, other related components; plant extract ratio), specifications: levels and range for markers, physico-chemical properties of relevant components; stability, purity criteria by chain control or analysis; microbiological, mycotoxins, pesticides, and environmental contaminants. Nature and level of excipients; formulation methodology, storage conditions should have been specified.

F. End product: formulated product.

G. Specification of the product.

H. Extent of use and estimated intake (posology and method of administration).

I. Bioavailability of active principles.

J. Toxicological assessment.

K. Preclinical and clinical studies. Clinical data including variability of response, adverse effects reports, and contraindications [78].

13. Possible ways to reduce the toxic effects of herbal products

Natural products/compounds are unique remedies, but as Paracelsus (1493–1541) stated that all substances are poison and this is just the correct dose that makes them medicine. There are some rules in the literature that can be summarized as follows:

a. If the herbal remedy is not prescribed by a registered physician, it should be considered unsafe.

b. The label and expiration date of the herbal products should be checked for the seal of the regulatory authority.

c. If the herbal medicine is consumed with allopathic medicines, the doctor should be informed.

d. Herbal products should not be used with drugs possessing narrow therapeutic index such as cyclosporin, digoxin, theophylline, and warfarin.

e. Herbal products containing heavy metals such as arsenic, lead, and mercury should not be used.

f. Pregnant or breastfeeding mothers should be careful when using herbal remedies such as black cohosh, chamomile, sage, Dong Quai root, feverfew, ginger, kava kava, St. John's wort, etc.

g. Excessive consumption of herbal/herbal medicine/natural products should be avoided and dosing instructions should be followed [3].

14. Conclusion

Herbal and traditional medicines are preferred as primary health care by three quarters of the world's population. Therefore, it is crucial in drug research to investigate the effectiveness and adverse effects of herbal medicine, to identify the active compounds in medicinal plants and to detect contamination from poisonous plants or herbal mixtures. In 2013, the World Health Organization (WHO) published the WHO traditional medicine strategy (2014–2023). It aims to support the use of Traditional Medicine (TM) and/or Complementary and Alternative Medicine (CAM) to improve public health, including phytotherapy using of medicinal product (MP) and/or herbal medicinal product (HMP) for medical practice. The plan aims to increase the safety, efficacy, and quality of TM and/or CAM by expanding its knowledge base and providing guidance on regulatory and quality assurance standards (WHO, 2013). In 2016, the National Complementary and Integrative Health Center (NCCIH) published a strategic plan to explore complementary

and integrative health science. This plan has been published to inform the public, healthcare professionals, and health policy makers, with evidence-based information about the usefulness and safety of complementary and integrative health interventions and their role in health care development. The plan uses key research to facilitate understanding of the biological effects, mechanisms of action, effectiveness, and clinical effects of complementary health approaches. Both the WHO and NCCIH plans aim to improve TM and CAM knowledge, including phytotherapy. Therefore, understanding herb-drug interactions and the molecular mechanisms involved in these processes is a way to guarantee safe use of MP and/or HMP. In addition, this can help therapeutic planning and healthcare professionals to recommend the best treatment strategy to use.

In this review, some critical issues are also discussed. The botanical identification and labeling of the plant material are important for preventing undesirable health problems. The changes in the scientific definitions of the plants in traditional medicine in time can cause unwanted or toxicologic effects by the usage of the wrong plant. The contamination of the plants with the environmental contaminants (microorganisms, fungal toxins such as aflatoxins, pesticides, and heavy metals), inappropriate preparation process, and interaction of traditional herbs by concomitant or consecutive usage also endanger the safety of herbal medicine for human health. What makes herbal medicine research valuable is that it has the chance to research harmful and toxic plants for developing pharmacologically and therapeutically worth remedies, and to develop medicinal plant combinations as safe and efficient herbal medicines. Standardization and strict control mechanisms are essential to maintain the high quality of herbal products and to prevent from the contaminations for the safety of patients [17].

The following guidelines can be suggested to minimalize the risk of herbal uses:

1. Should not be used in case of pregnancy or a possibility of pregnancy and to babies.

2. Should not be used when breast-feeding.

3. Should not be used as daily and in large amounts.

4. Should be bought from the pharmacies and only in case the plant names are stated on the packages and sealed by the Ministry of Health.

Do not believe it is useless if it is natural or it is harmless if it is natural [79].

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this chapter.

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Author details

Cigdem Kahraman[1], Zekiye Ceren Arituluk[2] and Iffet Irem Tatli Cankaya[2*]

1 Faculty of Pharmacy, Department of Pharmacognosy, Hacettepe University, Ankara, Turkey

2 Faculty of Pharmacy, Department of Pharmaceutical Botany, Hacettepe University, Ankara, Turkey

*Address all correspondence to: itatli@hacettepe.edu.tr

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