

Herbal Remedies in Global Health Care: Classification, Toxicology, and Clinical Management

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Purpose: Traditional herbal medicines are crucial in the health care system worldwide, particularly for individuals with chronic illnesses. These remedies are commonly classified by purpose, composition, mechanism of action, and origin, with the World Health Organization outlining 4 main categories: indigenous herbal medicines, those used in traditional systems, modified herbal medicines, and imported herbal products. The authors explored the toxicology of commonly used herbal remedies, including their mechanisms, signs and symptoms of toxicity, and treatment strategies.

Methods: Literature was searched using different published resources and databases, PubMed and ScienceDirect. The searched terms included “herbal medicine,” “herbal remedies,” “traditional medicine systems,” “herbal toxicity,” “herbal toxicity mechanism of action/toxicity,” among others. The searches were limited to the English language, with no restrictions on publication date.

Results: The perception that herbal medicines are inherently safe is misleading. Herbal remedies can be toxic due to the plant’s intrinsic properties or through contamination and adulteration. Moreover, 15%–20% of individuals on prescription drugs concurrently use herbal supplements, increasing the risk of harmful interactions. Incidence of herb-induced toxicities, particularly hepatotoxicity, is related to the use of Kava, Chaparral, Comfrey, Germander, and green tea extract. Moreover, cardiovascular toxicity due to Chan Su and oleander-containing herbal remedy use is detected by assessing serum digoxin concentration and is treated with Digibind. Although advances in modern formulations and increased regulatory oversight have improved safety, shortcomings remain, particularly in public awareness and standardized regulations.

Conclusions: Comprehensive clinical management, patient education, and integration of traditional medicine into mainstream health care ensures safe, effective, and responsible use of herbal products.

Key Words: herbal remedies, traditional medicine, traditional medicine systems, herbal toxicity

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INTRODUCTION

The World Health Organization (WHO) defines traditional medicine as the sum of knowledge, skills, and practices, based on theories, beliefs, and experiences from different cultures, used to maintain health and prevent, diagnose, improve, or treat illnesses. This term includes plant-, animal-, and mineral-based medicines, spiritual therapies, and manual or exercise-based techniques applied singly or in combination to promote well-being.¹

Similar to most medications, herbal remedies have been classified. The classification is based on numerous factors, such as their purpose (medicinal versus supplemental), chemical composition and additives, mechanism of action, plant origin, and parts used (leaves versus roots). The classification system was introduced by the WHO in 2003.² Herbal remedies are categorized into (1) indigenous herbal medicines, (2) herbal medicines in systems, (3) modified herbal medicines, and (4) imported products with an herbal medicine base.

Indigenous herbal medicines are traditionally used within specific communities or regions, and their composition, methods of use, and dosages are determined by long-standing cultural practices. Although formal documentation is often limited, these methods are widely accepted and used locally. However, once introduced to broader markets, they must comply with national safety and efficacy regulations. In contrast, herbal medicines from established traditional systems, such as Ayurveda, Unani, and Siddha, are well-documented and grounded in recognized theoretical frameworks endorsed by national authorities. Modified herbal medicines, which originate from traditional remedies but have undergone changes in formulation, dosage, or method of administration, must meet regulatory standards. Imported herbal products, whether raw materials or finished goods, must first be approved in their country of origin and adhere to the safety and efficacy requirements of the importing nation.³

Herbal remedies are classified according to their actions and the extent to which they affect different physiological systems within the body. They are classified as sedatives, antiseptics, or diuretics.⁴

The global herbal medicine market was valued at USD 148.5 billion in 2022 and is projected to reach USD 368.07 billion by 2032. This growth reflects the increasing consumer confidence in herbal remedies as alternatives to conventional pharmaceuticals. Contributing factors include perceptions of

greater effectiveness and relative affordability of herbal products.^{5,6}

Plants and herbal medicines are frequently perceived to be safe and harmless; however, this is a widespread misconception. Several plants contain bioactive compounds that can be toxic to humans, either on their own or when consumed alongside prescription medications. This misperception of safety has contributed to reports indicating that approximately 15%–20% of individuals taking prescription drugs also use herbal supplements,⁷ a practice that poses serious health risks. Herbal preparations are often used in combination and prepared using diverse methods, increasing the potential for contamination, adulteration, or presence of toxic compounds introduced during processing.⁸ Toxicity stems from contamination, adulteration, and intrinsic properties of the plants themselves. These risks underscore the significance of rigorous toxicological and safety evaluations to ensure safe use. This review examined the toxicology of globally recognized herbal medicines, outlining their known toxic effects, associated clinical signs and symptoms, available treatments, and health outcomes.

MATERIALS AND METHODS

The literature was searched using different published resources and databases, PubMed, and ScienceDirect. The search terms included “herbal medicine,” “herbal remedies,” “traditional medicine systems,” “herbal toxicity,” “herbal toxicity mechanism of action/toxicity,” among others. The search was limited to the English language, and there were no restrictions on the date of publication.

Global Overview of Herbal Remedies

Modern Herbal Formulations

Technological advances have transformed the use of herbal remedies, which traditionally involve preparing decoctions from different plant parts, such as seeds, leaves, stems, bark, roots, or flowers, into standardized, scientifically validated formulations, such as extracts, capsules, tablets, tinctures, and nano-formulations.⁹ These innovations have significantly improved the stability, bioavailability, efficacy, and safety profiles of herbal medicines, thereby facilitating their integration into modern health care systems and pharmaceutical development pipelines.^{9–11}

Unlike traditional decoctions, modern herbal formulations are characterized by standardized concentrations of the active constituents, reproducible pharmacological activity, and rigorous quality control processes. Advanced extraction techniques, such as supercritical fluid extraction, microwave-assisted extraction, and ultrasonic extraction, enable the selective isolation of bioactive compounds, reduce variability, and improve consistency between batches. Furthermore, the development of novel drug delivery systems, including liposomes, phytosomes, nanoparticles, and transdermal patches, has enhanced the targeted delivery, solubility, and absorption of phytochemicals.

In addition, modern formulations have been subjected to preclinical and clinical evaluations to establish their safety,

efficacy, and mechanisms of action. Regulatory agencies such as the European Medicines Agency and US Food and Drug Administration (FDA) have introduced frameworks for the approval of botanical drugs, further legitimizing herbal products within conventional therapeutic paradigms.

These advancements bridged traditional knowledge with modern science and addressed concerns regarding dosage accuracy, shelf life, contamination, and potential herb–drug interactions. Consequently, modern herbal formulations offer safer and more effective alternatives to traditional preparations, promoting greater consumer confidence and expanding their therapeutic applications in both preventive and curative health care.

Prevalence of Herbal Medicine Use

The use of herbal remedies is significantly higher among individuals with chronic illnesses compared to those without.¹² A US-based study investigating the prevalence of herbal medicine use among adults reported this association, and similar findings were observed in Ethiopia, where a high prevalence of use was also documented among chronically ill patients.¹³ The Ethiopian study further revealed that women and individuals living in rural areas were particularly likely to depend on herbal remedies. The consistency of these findings across the 2 countries on different continents suggests a broader global trend in reliance on herbal medicines among people with chronic diseases. This pattern reflected the influence of cultural beliefs, accessibility, affordability, and perceived efficacy on health-seeking behaviors. These insights highlight the need to integrate traditional medicines into mainstream health care systems, particularly in resource-limited settings, to support the safe, effective, and informed use of herbal products.

In South Africa, multiple studies have documented the widespread use of herbal remedies among people living with HIV/AIDS.^{14–16} Although these studies consistently reported the use of herbal treatments alongside antiretroviral therapy (ART), the proportion of concurrent users was relatively modest. Several individuals reported that they had used herbal remedies before initiating ART.^{15,16} Similar patterns have been observed among patients with cancer, where herbal products are often employed to alleviate symptoms, enhance quality of life, or as part of efforts to treat the disease.¹⁷ Nonetheless, concerns remain regarding the safety, efficacy, and potential interactions of these remedies with conventional medicines, particularly in the context of limited regulatory oversight.¹⁷

Several factors influence the decision to use herbal remedies, including cultural and traditional beliefs, dissatisfaction with conventional treatments, and a preference for more holistic or natural approaches to health. Furthermore, the affordability and accessibility of herbal products play significant roles in health care system worldwide. In several cases, individuals depend on recommendations from family members, community leaders, or traditional healers, especially in settings wherein trust in traditional knowledge systems remains strong. The widespread perception that natural products are safer or cause fewer side effects than pharmaceuticals further contributes to their use.¹⁸ However, without proper regulation and oversight, the use of herbal

remedies carries the risk of adverse effects or harmful drug interactions. These findings highlight the need for improved public health education and integration of traditional medicine into national health care frameworks to ensure the safe, effective, and responsible use of herbal therapies.

Common Toxic Herbal Remedies and Their Effects

Herbal remedies are widely regarded as effective, a perception supported by their long history of use and the scientific validation and commercialization of certain preparations. However, as Paracelsus, the “father of toxicology,” famously stated, “All things are poison, and none are without poison; only the dose determines that a thing is not a poison.” This principle underscores that toxicity depends not only on the nature of a substance but also on the quantity consumed. The same applies to herbal medicines, which, when prepared as traditional decoctions, may deliver inconsistent doses of active compounds owing to variations in preparation methods, plant parts used, or concentrations of bioactive constituents. Such variability increases the risk of toxicity or diminishes therapeutic efficacy, particularly when remedies are administered at high doses or are used frequently.¹⁹

The use of herbal remedies has grown substantially in recent years, accompanied by the continued introduction of new products and formulations in the market. However, the absence of stringent regulatory oversight has raised growing concerns regarding their safety and potential public health risks.¹⁸ Table 1 outlines the selection of plants that were later reported to exhibit toxic effects, while being widely used for medicinal purposes. Table 2 highlights 7 of the most commonly used traditional herbs that are known to possess inherent toxicities.

Several inherently toxic plants and herbs (Table 2) have been banned in multiple countries owing to safety concerns. In addition, reports of herbal-induced liver injury have increased over the last decade, with >12,000 publications documenting such cases between 2004 and 2020.⁷²

Hepatotoxic Herbal Supplements and Abnormal Liver Function Tests

Several herbal supplements are associated with hepatotoxicity, including commonly used products such as kava, comfrey, germander, chaparral, and green tea extracts. In several cases, abnormal liver function tests in otherwise healthy individuals are the first indication of herb-induced liver injury. Among these, kava, a herbal supplement traditionally used for its sedative and anxiolytic properties, is the most frequently cited. By 2003, 11 cases of hepatic failure were linked to kava use, of which 7 required liver transplantation and 4 resulted in death. Consequently, kava was banned in the European Union and Canada in January 2003, and the US FDA issued warnings regarding its safety. By 2009, >100 cases of kava-associated hepatotoxicity were reported.⁷³ Alcohol consumption is known to exacerbate kava-induced liver injury.

Kava contains 6 major kavalactones: methysticin, 7,8-dihydromethysticin, kavain, 7,8-dihydrokavain, yangonin,

and desmethoxyyangonin, which together account for approximately 96% of its total kavalactone content. Commercial preparations are typically ethanol- or acetone-based extracts, whereas traditional preparations in the South Pacific involve aqueous extractions.⁷⁴ Hepatotoxicity has been previously reported to be primarily associated with commercial solvent-based extracts, with traditional aqueous preparations considered safer. However, case studies and WHO reviews have demonstrated that aqueous kava extracts used in regions such as New Caledonia, Australia, the United States, and Germany may cause hepatotoxicity.⁷⁵

Contamination with toxic alkaloids further increased this risk. Pipermethysticin, found in kava leaves and stems, may enter preparations through poor quality control, whereas flavokavains, alkaloids present in kava roots, have also been implicated in toxicity. Hepatocellular injury occurred via mitogen-activated protein kinase signaling, leading to oxidative stress and apoptosis. The chemical composition of kava products, and, thus, their potential toxicity, varies according to factors such as plant age, plant parts used, cultivation conditions, and geographic origin.⁷⁶

Hepatotoxicity due to kava consumption is characterized by elevated serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase. In one documented case, a 50-year-old man who exceeded the recommended dose of 3 kava capsules daily for 2 months exhibited AST and ALT activities 60–70 times higher than the normal reference ranges. All hepatitis serology tests were negative, and kava consumption was identified as the cause of liver injury. The severity of the hepatotoxicity ultimately necessitated a liver transplant.⁷⁷

Comfrey (*Symphytum officinale*), a perennial plant traditionally used for wound healing, bone repair, and the treatment of conditions such as arthritis, gout, and psoriasis, lacks scientific evidence to support its use. Comfrey contains pyrrolizidine alkaloids that are potent hepatotoxins. Russian comfrey is more toxic than its European and Asian counterparts owing to its higher alkaloid content. Yeong et al described a case of a 23-year-old man who developed severe veno-occlusive disease and hypertension, ultimately dying from liver failure. Histological examination, including light microscopy and hepatic angiography, revealed occlusion of the sublobular veins and small venous radicles, accompanied by widespread hemorrhagic necrosis of hepatocytes, illustrating extensive liver damage linked to comfrey consumption. The patient, a vegetarian, had been using comfrey leaves as a dietary supplement.⁷⁸

Germander (*Teucrium chamaedrys*) is an aromatic plant belonging to the mint family (Lamiaceae). The flowers have traditionally been used in folk medicine to treat dyspepsia, diabetes, and gout. However, chronic germander consumption has been associated with hepatotoxicity. Toxic effects typically appear within 9 weeks of use and are characterized by jaundice and elevated activities of liver enzymes, particularly ALT and AST. Recovery after discontinuation of the herb may occur between 6 weeks and 6 months. The mechanism of toxicity is believed to involve the metabolism of diterpenoid compounds into more potent toxic intermediates.⁷⁹

TABLE 1. Plants Commonly Used as Traditional Remedies Later Found to Have Toxic Effects

Latin Name	Family	Common/ Vernacular Name	Traditional Use	Adverse Effects	Clinical Evidence	Possible Mechanisms of Toxicity
<i>Teucrium chamaedrys, T. polium, T. capitatum, T. viscidum</i>	Lamiaceae	Germanander	Dyspepsia, anorexia, nasal catarrh, chronic bronchitis, gout, rheumatoid arthritis, fever, uterine infections, wound healing, weight loss ²⁰	Increased serum activities of liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ glutamyl-transpeptidase (γ -GT), steatosis, hepatomegaly ²⁰ Several cases of liver disease (hepatitis), death ²¹	Thirty-five cases of hepatotoxicity, 2 of which were fatal and 4 causing chronic hepatitis ²¹ Capsules containing germanander, either alone or combined, are marketed as weight-control supplements and have been associated with hepatotoxicity as reported in about 30 cases from France ²² Toxicological studies demonstrated that one of the major furano neoclerodane diterpenoids, teucriin A, was implicated in the hepatotoxicity of germanander ²³	Activation of cytochrome P450 (mainly CYP3A) into reactive metabolites. The reactive electrophilic metabolites stimulate apoptosis by decreasing thiols (glutathione conjugate formation), increasing intracellular calcium ²⁴ Metabolic activation of teucriin A in rats results in extensive damage of numerous hepatic proteins (involved in lipid, amino acid, and drug metabolism, mitochondrial and peroxisomal enzymes) by covalent modification ²⁵ The formation of reactive metabolites may also cause immune reactions. ²⁶ Therefore, germanander-induced hepatotoxicity may be due to direct and secondary immune reactions
<i>Hypericum perforatum</i>	Hypericaceae	St John's wort	Anxiety, depression, and sleep disorders ²⁷	Dry mouth, dizziness, constipation, other GI symptoms, and confusion ²⁸	Long-term St John's wort administration resulted in a significant and selective induction of CYP3A activity in the intestinal wall. ^{27,29} Interactions with prescribed medicines, including warfarin, phenprocoumon, cyclosporin, HIV protease inhibitors, theophylline, digoxin, and oral contraceptives result in a decrease in concentration and, therefore, decreased efficacy ³⁰	Induction of CYP3A4, CYP2C9, and CYP1A2 activity and the transport protein P-glycoprotein. ^{27,29} St John's wort binds to the pregnane X receptor responsible for the expression of CYP3A4 ³⁰ Monoamine oxidase-inhibiting effects may cause increased levels of serotonin, dopamine, and norepinephrine ²⁷
<i>Ginkgo biloba</i>	Ginkgoaceae	Ginkgo	Improvement of cognitive functioning, ²⁹ memory loss, dementia, poor concentration, glaucoma, cerebral insufficiency, and peripheral circulatory disturbances	Precipitation of seizure ³¹ Spontaneous bleeding and may interact with anticoagulants and antiplatelet agents ²⁷	Two patients with controlled epilepsy presented with recurrent seizures within 2 weeks of commencing the extract of <i>Ginkgo biloba</i> ³¹ A fatal seizure in a 55-year-old man due to potential herb-drug interactions with <i>G. biloba</i> ³²	Induction of CYP2C19 is responsible for the metabolism of several anticonvulsant medications, resulting in subtherapeutic concentrations of the medication, thereby precipitating seizures and possibly causing death. ^{32,33} Ginkgolides, biologically active constituents of <i>G. biloba</i> , are potent inhibitors of platelet aggregating factors, resulting in increased vasodilation and peripheral blood flow rate, leading to serious adverse effects such as prolonged

TABLE 1. (Continued) Plants Commonly Used as Traditional Remedies Later Found to Have Toxic Effects

Latin Name	Family	Common/ Vernacular Name	Traditional Use	Adverse Effects	Clinical Evidence	Possible Mechanisms of Toxicity
<i>Thevetia peruviana</i>	Apocynaceae	Yellow oleander	Antibacterial, antifungal, ³⁶ abortifacient, diuretic, cardiotonic, emetic, and purgative ³⁶	Gastrointestinal and cardiac symptoms, local irritation of mucous membranes, nausea, vomiting, severe diarrhoea, abdominal pain, dilated pupils, and convulsions ³⁶ Cardiovascular manifestations range from sinus bradycardia with sinoatrial block to first and second-degree heart block, junctional rhythms, A–V block, atrial and ventricular ectopic beats, and ventricular fibrillation. ^{36,37}	168 cases of human poisoning in Sri Lanka ³⁷	Cardiac glycosides exert a digoxin-like effect by inhibiting the sodium-potassium adenosine-triphosphatase (ATP) enzyme systems The increased intracellular sodium concentration and the increased serum potassium concentration produce a negative chronotropic and positive inotropic effect ³⁸ The resulting toxic syndrome resembles digitalis poisoning with marked hyperkalemia, conduction abnormalities, and ventricular arrhythmias ³⁹

A recent case report described a 45-year-old hypertensive woman who consumed 3 cups of boiled *Teucrium polium* (Felty germander) in an attempt to induce abortion and was subsequently hospitalized. She presented with abdominal pain, weakness, lethargy, nausea, fever, chills, anorexia, and hematuria. Laboratory tests revealed severe hemolysis (lactate dehydrogenase, 3903 U/L) and a rapid drop in hemoglobin to 4.7 mg/dL within 12 hours. Additional findings included marked increases in the white blood cell count, reticulocyte count, blood urea nitrogen, and creatinine levels. A peripheral blood smear demonstrated +3 schistocytes and acanthocytes. Viral markers and direct and indirect Coombs tests were negative. The patient was diagnosed with acute intravascular hemolysis accompanied by renal failure. With supportive treatment, including blood transfusions and intravenous hydration, her liver and kidney functions gradually improved, and she was ultimately discharged.⁸⁰

Chaparral (*Larrea tridentata*), a plant native to the Southwestern United States and Northern Mexico, has traditionally been used as an herbal remedy for different ailments, ranging from cold sores to muscle pain. However, its use has been linked to severe hepatotoxicity, as evidenced by multiple reports of chaperone-associated hepatitis. Sheikh et al reviewed 18 cases of suspected central toxicity reported by the FDA and confirmed 13 cases of herb-induced liver injury. Clinical manifestations, typically jaundice with marked elevations in liver enzymes, appear between 3 and 52 weeks after chaparral ingestion and resolve within 1–17 weeks after discontinuation in most cases. Toxic or drug-induced cholestatic hepatitis is the predominant cause of liver injury. Among the reported cases, 4 progressed to cirrhosis, whereas 2 experienced acute fulminant liver failure necessitating liver transplantation.⁸¹

Pennyroyal (*Mentha pulegium*) is a mint family plant whose leaves emit a spearmint-like aroma when crushed. This fragrance is used in bath products and aromatherapies. Traditionally, pennyroyal has been consumed in small amounts as tea because of its abortifacient and emmenagogue properties. Plants and their essential oils contain several bioactive compounds, of which pulegone is the primary constituent. Pulegone is metabolized into the more toxic compound menthofuran in the liver and can deplete hepatic glutathione stores in a manner similar to an acetaminophen overdose.

Anderson et al reported 4 cases of pennyroyal ingestion, one of which resulted in death. Postmortem serum analysis revealed pulegone and menthofuran concentrations of 18 and 1 ng/mL, respectively. Notably, N-acetylcysteine, commonly used as an antidote for acetaminophen poisoning, was successfully used to treat one of the surviving patients, whereas the other 2 patients, who ingested minimal amounts, did not require this intervention. The authors also reviewed 18 additional cases of pennyroyal toxicity, concluding that ingestion of as little as 10 mL of pennyroyal oil can cause severe poisoning.⁸² Gordon and Khojasteh⁸³ further noted that most reported cases of pennyroyal toxicity and fatalities occurred in women who used the herb for its abortifacient effects.

Green tea (*Camellia sinensis*) contains bioactive polyphenolic compounds, known as catechins, including epicatechin, epigallocatechin, gallocatechin, epicatechin gallate, and epigallocatechin-3-gallate (EGCG), which are potent antioxidants. Although moderate consumption of green tea (2–3 cups per day) is generally considered safe and beneficial, higher concentrations of EGCG, the primary active

TABLE 2. Inherently Toxic Herbs, Their Common Use, Mechanism of Injury Including the Clinical Presentation of Poisoning With These Herbs and Treatment

Herb	Common Use	Inherent Toxicity	Mechanism of Toxicity/Injury	Signs and Symptoms	Treatment
Kava (<i>Piper methysticum</i>)	Anxiety, sleep disorders. ^{40,41}	Hepatotoxicity. ^{42,43}	Inhibits some cytochrome P450 isoenzymes, and CYP 2E1,43 herb–drug interaction, ⁴⁴ glutathione depletion ⁴⁵	Fatigue, liver failure, nausea, vomiting, ⁴⁴ elevated liver enzymes ⁴⁶	Liver transplant and discontinue use ⁴⁷
Ephedra (Ma Huang)	Weight loss, performance enhancement, mental acuity, allergies, asthma, etc. ^{42,48}	Cardiovascular toxicity and idiosyncratic liver injury, ⁴² elevated blood pressure ⁴⁹	Sympathomimetic stimulation via ephedrine alkaloids ⁵⁰	Hypertension and palpitations, ⁴⁹ myocardial infarction ⁵⁰	
<i>Aristolochia</i> spp.	Seizure prevention, elevates libido, boosts the immune system, and starts menstruation ⁵¹	Nephropathy ^{52,53} and carcinogenicity. ^{52,54}	Plants contains aristolochic acid, which leads to the formation of DNA adducts. ^{55,56}	Renal failure, gastrointestinal abnormality, anemia, hypertension, ⁵⁷ urothelial cancers ⁵⁸	Discontinue use, dialysis, and kidney transplant in severe cases ⁵⁸
Comfrey (<i>Symphytum</i> spp.)	Wound healing, alleviates joint pain and inflammation. ^{59–61}	Hepatotoxicity, ⁴² carcinogenicity ⁶²	Pyrrrolizidine alkaloids damage the hepatic endothelial cells and can cause sinusoidal obstruction ⁴²	Right upper quadrant pain, nausea, fluid retention, and jaundice ⁴²	Avoid continued use; treatment should target associated clinical problems ⁶³
Aconite (<i>Aconitum</i> spp.)	Pain, rheumatism, and lethargy ⁶⁴	Toxicosis, cardiotoxic and neurotoxic effects, ⁴⁰ ventricular tachyarrhythmia, and heart arrest ⁶⁵	Interference with cellular metabolic pathways, interference with microRNA expression, modulating calcium channels, sodium potassium ATPase pumps, and decreasing acetylcholine release ⁶⁶	Ventricular tachycardia, mild gastrointestinal effects, from seizures, and fatal dysrhythmias ⁶⁶	Gastric decontamination with activated charcoal if ingested and supportive care ⁶⁶
Pennyroyal (<i>Mentha pulegium</i>)	Purifying blood, headaches, hoarseness, nausea, soothe bruises, clear spots, ⁶⁷ induce abortion ⁶⁸	Acute liver injury, cardiovascular collapse, coupled with intravascular coagulation ⁴²	The plant contains pulegone, which is converted by the cytochrome P450 system (CYP 1A2 and 2E1) to other hepatotoxins (menthofuran), therefore, inducing liver and multiorgan injury ⁴²	Abdominal pain, nausea, vomiting, lethargy, and agitation ⁶⁸	Discontinue use
Chaparral (<i>Larrea tridentata</i>)	Cancer, arthritis, tuberculosis, skin conditions, and the cold. ^{69,70}	Hepatotoxicity ^{42,70}	Nordihydroguaiaretic acid affects intrahepatic pathways ⁴²	Jaundice, fatigue, liver enzyme elevation ⁷¹	Discontinue, monitor liver function, supportive treatment

compound, can be hepatotoxic at higher concentrations. Products such as weight-loss supplements (eg, Slim Quick) contain concentrated green tea extracts, and regular consumption of these high-dose preparations is associated with liver toxicity.⁸⁴

Numerous herbs have been associated with liver injury. For instance, skullcap (*Scutellaria lateriflora*) is traditionally used as a sedative and calming agent and is recommended for conditions such as nervous tension, epilepsy, and hysteria. Several reports of hepatotoxicity have involved skullcap taken in combination with other herbs, including valerian and *Ginkgo biloba*. Black cohosh (*Cimicifuga racemosa*) has been implicated in liver toxicity.⁸⁵

Gotu kola (*Centella asiatica*, Sanskrit: Mandukaparni), a staple in Indian Ayurvedic medicine for managing hypertension and promoting wound healing, contains pentacyclic triterpenic saponosides, such as asiaticoside and madecassoside, which may contribute to hepatotoxic effects. In one study, 3 women aged 61, 52, and 49 years presented with markedly elevated liver enzyme activities: ALT values of 1193, 1694, and 324 U/L; ALP values of 503, 472, and 484 U/L; and bilirubin levels of 4.23, 19.89, and 3.9 mg/dL, respectively. All patients showed improvement after the discontinuation of herbal medication.⁸⁶

Application of Digoxin Immunoassays to Detect Herbal Toxicity

Chan Su is a traditional Chinese medicine derived from dried white secretions of the auricular and skin glands of the Chinese toad (*Bufo melanostictus* or *B. gargarzinus*). It is a key ingredient in other Chinese formulations, such as Liu-Shen-Wan and Kyushin, which are used to promote cardiac health. The cardiotonic effects of Chan Su are primarily attributed to bufadienolides such as bufalin, cinobufagin, and resibufogenin. Bufalin is known to increase vasoconstriction, vascular resistance, and blood pressure, possibly by inhibiting the Na⁺/K⁺-ATPase activity. High doses of Chan Su can induce cardiac arrhythmias, seizures, and coma, with fatalities reported. For instance, a woman died after consuming Chinese herbal tea containing Chan Su.⁸⁷

Ingestion of Chan Su can also result in digoxin-like immunoreactivity in the serum owing to the structural similarities between bufalin, cinobufagin, and digoxin. Panesar⁸⁸ reported a fatal case in which a woman who consumed Chan Su had a digoxin level of 4.9 ng/mL. Consequently, the detection of digoxin in a patient not taking the drug may serve as an indirect marker of Chan Su poisoning.

Oleanders (*Nerium oleander* and *Thevetia peruviana*) are evergreen ornamental shrubs with pink, white, or bright

yellow flowers that grow in the tropical and subtropical regions worldwide. All parts of these plants were toxic. Yellow oleander (*T. peruviana*) contains at least 8 toxic cardiac glycosides, including thevetin A, thevetin B, thevetoxin, nerifolin, peruvoside, and ruvoside, whereas the cardiotoxicity of pink or white oleander (*N. oleander*) is primarily attributed to oleandrin. Notably, oleandrin is resistant to inactivation by boiling and drying. Deliberate oleander ingestion is a common method of suicide in Sri Lanka, with an estimated fatality rate of approximately 10%. Both plants have been used as herbal preparations to promote cardiac health. The measurement of apparent digoxin concentrations using a digoxin immunoassay in patients not taking digoxin can aid in the diagnosis of oleander poisoning.³⁴

Heavy Metal Toxicity in Chinese Herbal and Indian Ayurvedic Medicines

Heavy metals and pesticides are common contaminants in Chinese herbal medicines. Harris et al analyzed 334 samples of Chinese herbal products and found that every sample contained at least one heavy metal (lead (Pb), arsenic (As) chromium (Cr), mercury (Hg), or cadmium (Cd)), whereas 115 samples (34%) had detectable levels of all 5 metals. In addition, 42 pesticides were detected in 108 samples (36.7%).⁸⁹

Zuo et al⁹⁰ measured the concentrations of Pb, Cd, As, Hg, and Cu in 2245 batches of Chinese herbal medicines using inductively coupled plasma-mass spectrometry and reported mean concentrations of 1.566, 0.299, 0.391, 0.074, and 8.386 mg/kg, respectively, of Pb, Cd, As, Hg, and Cu. Similarly, Yang et al evaluated 10,245 samples across 279 types of Chinese herbal medicines for toxic heavy metals using a validated inductively coupled plasma-mass spectrometry method. The analysis identified high-risk contamination in specific herbs: Pb in *Cibotti* rhizome, *Selaginellae herba*, *Morinda officinalis* radix, *Asprellae ilicis* radix, and *Toxicodendri resina*; As in *Eckloniae/Laminariae thallus*, *Spirodelae herba*, and *Naturalis indigo*; Cd in *Tetrapanaxis medulla*, *Centipedae herba*, *Cyathulae radix*, *Linderae radix*, *Mereticis/Cyclinae concha*, and *Tabanus*; and Hg in *T. resina*.⁹¹

Heavy metal toxicity caused by herbal products has been previously documented. For instance, a 30-year-old Indian sailor developed microcytic anemia (Hb 9.9 g/dL), persistent abdominal pain, vomiting, dark stools, hyperchromic urine, latent jaundice, and asthenia after consuming Ayurvedic medicine. Blood analysis confirmed severe lead intoxication (blood lead level of 102 mcg/dL), and the patient was treated with chelation therapy. Subsequent analysis of the Ayurvedic preparations revealed high levels of lead.⁹² Arsenic poisoning after the consumption of Indian Ayurvedic medicines has also been reported.⁹³

Herbal Supplements Contaminated With Western Drugs

Another significant source of herbal medicine toxicity is adulteration by undisclosed Western pharmaceuticals. These synthetic drugs are not listed on product labels,

creating serious risks of toxicity. For instance, in one study that analyzed 2069 samples of traditional Chinese medicines collected from 8 hospitals in Taiwan, undeclared pharmaceuticals were detected in 618 samples (23.7%). The most common are caffeine, acetaminophen, indomethacin, hydrochlorothiazide, and prednisolone.⁹⁴ Several of these products are marketed for pain relief, inflammation, or arthritis management, which can be achieved by the adulterants themselves. Of particular concern is the presence of corticosteroids, such as prednisolone, which carry significant risks when used without medical supervision.

Butibutramine, an oral anorexiant, is another commonly reported adulterant in herbal slimming products and dietary supplements.⁹⁵ A case report described a 33-year-old woman with an 8-year history of epilepsy treated with valproate, carbamazepine, and phenobarbital, but never with phenytoin. After the use of 3 proprietary Chinese medicines, in addition to her prescribed therapy, she presented with toxic phenytoin levels (48.5 mg/mL). Laboratory analyses revealed that one preparation (Jue Dian Shen Ying Wan, orange capsules) contained 41 mg phenytoin, despite the manufacturer claiming that the capsules contained only Chinese herbal ingredients for epilepsy management.⁹⁶

Similarly, Savaliya et al reported adulteration of Indian Ayurvedic medicine. Of the 58 products analyzed, 10 contained undeclared steroid or nonsteroidal anti-inflammatory drugs. Dexamethasone and diclofenac were the most frequently detected drugs, whereas piroxicam was found in one preparation and dexamethasone in the other.⁹⁷

Clinical Management of Herbal Toxicity General Management Principles

In most countries, herbal remedies are usually obtained over the counter, rather than by prescription or purchased from informal markets. Some patients may require a prescription; however, this depends on the regulatory framework and specific herbal product. For the latter, pharmacists play a vital gatekeeping and advisory role in ensuring safe use, preventing harmful interactions, and promoting evidence-based decision making in health care.

Effective management of potential herbal toxicity begins with a comprehensive clinical assessment. This process should begin with a detailed history-taking, which involves gathering information about the specific herbal products or products consumed. Clinicians should attempt to obtain the botanical name, if known, and the brand or source of the product, method of preparation, dosage, frequency, and duration of use, and whether the herbal remedy is used in combination with other medications or substances.

A thorough physical examination is essential and should focus on identifying any signs of systemic toxicity. Particular attention should be paid to the potential involvement of hepatic, renal, cardiovascular, and neurological systems, which are often affected by herbal toxicity.

Baseline investigations should be conducted to support clinical assessments. These may include tests such as liver and renal function panels, serum electrolytes, complete blood count, coagulation profiles, urinalysis, and

electrocardiography. The choice of test depends on the clinical presentation and type of suspected toxicity.

Clinicians should maintain a high index of suspicion when evaluating patients with unexplained symptoms, particularly in those with a history of herbal product use. Prompt identification of the causative agent and immediate discontinuation are crucial steps to prevent further harm and improve clinical outcomes.

Symptomatic and Supportive Treatment

In most cases of herbal toxicity, management is primarily supportive and guided by the patient's presenting symptoms, because specific antidotes for several herbal toxins are unavailable. The symptomatic care focuses on minimizing further harm, stabilizing the patient, and supporting the affected organ systems.

Gastrointestinal decontamination is one of the initial steps in some cases. If a toxic herb is ingested, the patient presents within the first hour, is clinically stable, and the substance is known to benefit from decontamination, activated charcoal may reduce systemic absorption.

Hydration and electrolyte management are critical care components. Intravenous fluids should be administered to maintain adequate perfusion, and electrolyte imbalances must be corrected, especially in patients with vomiting, diarrhea, or signs of renal involvement.

Specific support strategies must be implemented in cases of organ dysfunction. In cases of hepatotoxicity, liver enzyme and bilirubin levels should be closely monitored. Referral to a hepatologist or evaluation for liver transplantation may be necessary if the liver injury is severe. Ensuring adequate hydration is essential to prevent nephrotoxicity, and renal function should be regularly assessed. Dialysis was indicated if renal failure developed.

Cardiotoxicity requires continuous electrocardiography monitoring, appropriate management of arrhythmias, and hemodynamic support where necessary. In patients exhibiting neurotoxicity, seizures should be controlled using benzodiazepines, and clinicians should assess for signs of altered mental status or encephalopathy.

Inhaled corticosteroids may be required for critically ill patients, particularly those with respiratory compromise or unstable blood pressure. These include mechanical ventilation and vasopressor therapy to maintain adequate oxygenation and perfusion. Overall, the management approach should be individualized and responsive to specific clinical manifestations and toxicity severity.

Use of Specific Antidotes

Although specific antidotes for herbal toxins are generally limited, they can be employed in situations where the causative agent has been identified. When available and appropriate, antidotes play crucial roles in mitigating toxicity and improving patient outcomes.

N-Acetylcysteine is an antidote commonly used in cases of liver injury, particularly when the clinical presentation resembles that of paracetamol toxicity. It may also be beneficial in cases of hepatotoxicity resulting from herbal products, such as *T. chamaedrys* (Germander) or *Polygonum multiflorum* (Chinese

knotweed). Atropine is indicated in situations involving anticholinergic poisoning or bradyarrhythmias caused by herbs containing alkaloids, such as *Atropa belladonna* (deadly nightshade). Its administration counteracted the muscarinic effects of these toxins. In cases of cardiac glycoside toxicity, particularly from herbal sources such as *Digitalis purpurea* (foxglove) or *T. peruviana* (yellow oleander), digoxin-specific antibody fragments (Digibind) may be considered. These antibodies can neutralize toxic effects and support cardiac stabilization. Physostigmine may be used to reverse central anticholinergic toxicity; however, considering its potential for serious adverse effects, it should be administered with extreme caution, ideally under the guidance of a toxicologist.

Despite the presence of specific antidotes, no targeted therapy is available in several instances. In such cases, management must depend entirely on supportive care and vigilant monitoring tailored to the patient's clinical status and affected systems.

Role of Toxicology Services and Poison Control Centers

Consultation with a poison control center or clinical toxicologist can provide real-time evidence-based guidance on risk assessment, the need for hospital admission, decontamination strategies, and antidotal therapy. These services are particularly helpful when dealing with unfamiliar herbs or when plant misidentification is suspected.

Patient Education and Prevention

Preventive strategies are essential to reduce the risk of recurrent herbal toxicity and promote the safe use of herbal products. Therefore, patient education is an important measure. Clinicians are responsible for informing patients about the potential risks associated with the use of herbal supplements, particularly when taken with prescription medications. Several herbal products interact with conventional drugs, causing adverse effects or reduced therapeutic efficacy.

Creating an open and nonjudgmental environment wherein patients feel comfortable disclosing all forms of alternative therapies is essential. Encouraging transparency during medical consultations enables clinicians to identify potential risks early and provide appropriate guidance.

In addition, patients should be made aware of the lack of standardization and regulations for the production and marketing of herbal products. Unlike pharmaceutical drugs, herbal remedies are often not subjected to rigorous quality control, causing variability in their composition, contamination, or mislabeling. Clinicians should advise patients to use only well-researched and reputable formulations, ideally those that have undergone safety evaluations or are supported by scientific evidence.

Health care providers safeguard patients from future episodes of herbal toxicity by integrating these preventive approaches into routine clinical practice and promoting the use of complementary therapies.

CONCLUSIONS

Although herbal remedies offer valuable therapeutic benefits and are widely used worldwide, their potential

toxicity and harmful interactions cannot be overlooked. Advances in modern formulations and increased regulatory oversight have improved safety; however, gaps remain, particularly in public awareness and standardized regulations. Comprehensive clinical management, patient education, and integration of traditional medicine into mainstream health care are essential to ensure the safe, effective, and responsible use of herbal products. Ongoing research and collaboration between traditional and modern medical systems are the keys to maximizing the benefits of herbal therapies while minimizing the associated risks.

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