A Review of the Toxicity of Compounds Found in Herbal Dietary Supplements

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ABSTRACT

Use of herbal dietary supplements by the public is common and has been happening for centuries. In the United States, the Food and Drug Administration has a limited scope of regulation over marketed herbal dietary supplements, which may contain toxic botanical compounds that pose a public health risk. While the Food and Drug Administration has made efforts to prohibit the sale of unsafe herbal dietary supplements, numerous reports have proliferated of adverse events due to these supplements. This literature review investigates bioactive plant compounds commonly used in herbal dietary supplements and their relative toxicities. Using primarily the National Library of Medicine journal database and SciFinder for current reports, 47 toxic compounds in 55 species from 46 plant families were found to demonstrate harmful effects due to hepatic, cardiovascular, central nervous system, and digestive system toxicity. This review further contributes a novel and comprehensive view of toxicity across the botanical dietary market, and investigates the toxicity of the top ten botanical dietary supplements purchased in the United States of America to gauge the exposure risk of toxicity to the public. The criteria of measuring toxicity in this review (plant compound, family, quantity, and toxicity effects) across the entire market in the United States, with special attention to those supplements whose exposure to the consumer is maximal, provides a unique contribution to the investigation of botanical supplements.

Introduction

Herbal medicine has been used for centuries to cure illness and to improve quality of life. The practice of herbal medicine continues to be important in the culture of communities across the globe. An estimated four billion people living in developing countries (80% of the world's population) depend upon herbal medicine as a primary healthcare source [1]. The use of herbal medicine in highly developed countries has increased in recent years as healthcare costs rise. Individuals have begun to self-medicate with herbal supplements, complement their traditional practices, or utilize alternative practices such as Chinese herbal medicine, Ayurvedic medicine, and homeopathy [2].

In the 1990s, herbal medical drugs represented 40% of all healthcare services delivered in China. In other countries, an esti-mated 48% (Australia), 70% (Canada), 42% (USA), 38% (Belgium), and 75% (France) of each respective nation's population had used herbal drugs at least once [1]. In a 2007 NHIS report, almost 40% of adults surveyed had used alternative medical therapy in the past year. Survey results showed that alternative medicine was commonly used to treat back pain, head or chest colds, neck pain, joint pain, anxiety, or depression. The most commonly used alternative medical therapy was consuming "nonvitamin, nonmineral, natural products". Some of the most popular herbal products used were *Echinacea*, ginseng, *Ginkgo*, and saw palmetto [3]. These nonvitamin, nonmineral, natural products account for the majority of out-of-pocket expenses for alternative medicine. In

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ABBREVIATIONS

ALT	alanine aminotransferase
AMI	acute myocardial infarction
DSHEA	Dietary Supplement Health and Education Act
EBSCO	Elton B. Stephens Co
EGCG	epigallocatechin gallate
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FSMA	Food Safety Modernization Act
HDSs	herbal dietary supplements
MTCA	(1R,3S)-1-methyl-1,2,3,4-tetrahydro-[beta]-carboline-3-carboxylic acid
NDGA	Nordihydroguaiaretic acid
NHIS	National Health Interview Survey
PubMed	National Library of Medicine journal database
SGPT	serum glutamic pyruvate transaminase
SGOT	serum glutamic oxaloacetic transaminase
TEG	triethylene glycol
USA	United States of America

the 2007 NHIS report, those who use alternative medicine spent $14.8 billion on these products [4].

In the USA, sales have increased by $6 billion between 2007 and 2012. Furthermore, the botanical dietary supplement market in the USA is expected to increase further in worth by 2020 as disease prevention and healthier living becomes a top concern for many Americans [5].

This industry is regulated to a limited extent in the USA. Congress passed the DSHEA of 1994 to amend the 1958 Food Additive Amendments of the Federal Food Drug and Cosmetic Act. Due to this act of legislation, many dietary supplements contain ingredients not recognized by DSHEA as a traditional nutrient, thus, allowing dietary supplement manufacturers to bypass FDA regulations [2].

Before new drugs and food additives are released on to the market, they must undergo lengthy, rigorous testing to prove product safety and efficacy. Product efficacy is investigated through human trials to demonstrate that the product will have the claimed effect on its label. These tests, along with the expense of applying to the FDA, are quite costly, and this cost presents itself to the customer at the retail counter. Botanical dietary supplement manufacturers are not mandated to undergo FDA testing; thus, this is a cost saving to the manufacturer and customer. Botanical supplements are generally much less expensive than Western medicine, providing another reason for botanical dietary supplements to be an attractive alternative or complement to Western medicine.

However, in 2011, the FSMA was passed and raised the safety standards for new ingredients in dietary supplements. Dietary supplement manufacturers must notify the FDA in advance when a new dietary ingredient will be included in a product. Dietary supplement manufacturers must now provide evidence of safety of any new dietary ingredients in order to prevent consumer health from being put at risk [6].

Although supplement manufacturers are not mandated to undergo FDA testing, manufacturers are recommended to provide scientific evidence to support any claims made in product labeling and advertisements. Since DSHEA was passed in 1994, the FDA has identified problems with supplements, and manufacturers have warned about and recalled possible harmful products [2], such as *Aristolochia* and comfrey. In 2004, botanical supplements containing ephedrine alkaloids were banned by the FDA due to the increased risk of stroke, heart attack, and death [7].

Furthermore, the FDA has also issued advisories on entire families of dietary supplements containing specific active ingredients. For example, the FDA issued an advisory in 2014 warning all manufacturers of supplements containing comfrey, a plant discussed in this literature, to remove this ingredient from their products. According to the FDA, the pyrrolizidine alkaloids within the herb show substantial evidence for hepatotoxicity and therefore are unsafe for ingestion [8]. This advisory proves the necessity for research and literary review in identifying hazardous dietary supplement ingredients that may call the FDA to attention and implement reform to their distribution.

Despite this increased risk, the general public, both in the USA and across the world, views herbal medicine as a natural approach to healing. Many assume these natural products are not toxic, and do not consider the possible adverse effects of improper use and unrestrained intake. Some of the botanical supplements used as herbal medicine are derived from plants not typically used for human consumption. Therefore, the safety and efficacy of these plants remain untested. For example, saw palmetto extracts have been shown to improve male urological symptoms with low adverse events compared to the prescription drug finasteride used to treat these symptoms. However, the long-term effects and overall effectiveness have yet to be determined [2]. Additionally, the increase in herbal product usage in populations that also have ready access to conventional medicines (drugs) and polypharmacy warrants more consideration of the potential for herb-drug interactions [9].

The lack of information among botanical dietary supplement manufacturers coupled with the general public's lack of risk awareness can lead to the development of severe poisoning and acute health problems in herbal medicine users [1].

In this literature review, we have compiled 49 known toxic compounds present in 53 different plant species belonging to 39 plant families with various adverse effects such as hepatotoxicity, cardiovascular toxicity, and central nervous system effects. The purpose of this review is to provide a succinct summary of known toxicity levels, usage limits, and possible health risks associated with medicinal plants and extracts derived from plants ranging across the entire herbal supplement market. Furthermore, the potential toxicity levels have been investigated for the top ten botanical dietary supplements available to consumers in the USA in order to more accurately gauge the public consumer's exposure to these toxicities. As more toxic compounds in herbal medicine undergo testing and more data becomes available through academic research, supplement manufacturers can make safer products, and the general public can make more informed health decisions.

Methods

To compile this literature review, PubMed, EBSCO, and SciFinder (▶ Table 1) were primarily used to conduct searches about toxicity levels of plant compounds found within botanical dietary supplements and herbal drugs. Various search terms such as "toxic plant compounds", "herbal supplement adverse effects", "plant compound adverse effects", "toxic herbal medicine", "toxic botanical supplements", and "toxic alternative medicine" were used to maximize results. Furthermore, the scientific names of the top ten botanical dietary supplements on the market were paired with these terms to investigate the potential toxicity of products most frequently consumed by the public. These include: *Curcuma longa, Triticum aestivum, Linum usitatissimum, Aloe barbadensis, Sambucus nigra, Silybum marianum, Lepidium meyenii, Withania somnifera, Echinaceae* spp., and *Serenoa repens* [10]. If another source suggested that a specific plant species or plant compound had possible toxicity, PubMed was utilized to verify the claim by searching "(suggested plant or compound) AND toxic". If several journal articles corroborated the claim, the plant compound was included in the review. The majority of sources were derived from articles published in the past ten years (since 2007), while one source was published in 1984 and another source was published in 1976.

For a plant compound to be included in the review, these four elements were considered vital:

- An identifiable compound within the plant species or botanical dietary supplement that has been connected to the toxic effects observed
- The identity of the plant family and species from which the toxic compound originates
- The amount of the plant compound/plant species/botanical dietary supplement that was consumed when the toxic effects were observed
- A description of the toxic effects observed

Many articles lacked one or more of the elements described above. When this occurred, attempts were made to find the missing information through other database searches and using plant toxicology reference books to identify compounds and their levels in plant species. Several sources, however, had to be excluded from the study due to lack of compliance to at least one of the aforementioned criteria.

Secondary sources for this literature review included plant toxicology textbooks, reports from U. S. and European federal agencies, and databases such as NAPRALERT. Two tables have been created from the sources accumulated from this review to organize the information resulting from the aforementioned searches: one table detailing the potential toxicity levels from adverse events of the top ten most sold botanical dietary supplements on the US market, and another table detailing the information obtained from sources regarding the toxicity of plant compounds across the botanical supplement market (▶ Tables 2 and 3, respectively).

▶ **Table 1** Sources used in the literature search.

Databases	Agency websites	Books
• LiverTox • NAPRALERT • PubMed • TOXNET • EBSCO	• European Medicines Agency (EMA) Committee on Herbal Products • NIH National Center for Complementary and Integrative Health • U. S. Food and Drug Administration (FDA)	American Herbal Products Association's botanical safety handbook (2nd ed.)

Results

The possible toxic compounds were placed into categories based upon their effects. The most common effect was hepatotoxicity (15 compounds) followed by cardiovascular toxicity (12 compounds), digestive system toxicity (5 compounds), nervous system toxicity (6 compounds), renal toxicity (4 compounds), reproductive toxicity (3 compounds), endocrine toxicity (1 compound), and dermatological toxicity (1 compound) (▶ Tables 2 and 3). Twenty-three human trials and twenty-seven animal studies were accumulated in this search.

Plants and plant constituents associated with hepatotoxicity

The fifteen compounds known to be hepatotoxic are present in 20 plant species and 16 plant families. The anthraquinone emodin was found to be the most toxic of these compounds. Emodin is present in *Frangula alnus* Mill., a member of the Rhamnaceae family, and *A. barbadensis* Miller, commonly called aloe vera, a member of the Asphodelaceae family. Hepatocyte viability decreased by 30–45% when mice were orally given 40 and 80 µM of pure emodin extract for 24 h [11]. Clinical reports of acute toxic hepatitis in humans have been reported [12–14]. Although, two research teams suspect that a hypersensitive immune response is responsible for the induction of hepatitis due to the patients' elevated levels of eosinophils [12, 14]. However, one clinical case study detailed a woman's development of hepatitis after orally consuming 500 mg of aloe vera leaf powder every 2–3 days for 5 years. After being admitted to the hospital and stopping the consumption aloe vera, her liver function returned to normal [12].

Overconsumption of emodin has been shown to elevate liver enzyme concentrations along with other adverse effects, such as seizures, nephritis, gastrointestinal hemorrhage, and dyspnea. However, the genus *Senna* contains emodin, and a maximum daily oral intake has been established for senna-based products at 34.4 mg [15]. *In vitro* studies suggest that emodin significantly inhibits critical pathways in these cells, such as Toll-like receptors, MAPK, and NF-*κ*B pathways [16].

According to the National Center for Complementary and Integrative Health [17], *Ginkgo biloba* L. of the Ginkgoaceae family, and commonly known as ginkgo, has not been linked to liver injury. Sometimes, ginkgo has even been used to treat various forms of liver injury. As stated previously, ginkgo can inhibit liver

▶ **Table 2** Toxicity occurrences of top ten botanical dietary supplements sold on the US market*.

Compound name and structure	Plant name/family	Plant part	Sample type/route of administration/dosage/% of constituents	Test organism	Side effects	Toxicity category	References
Anthraquinones	Aloe barbadensis Miller/Asphodelaceae	whole leaf	extract/oral/100 mg/kg	rat	reproductive toxicity, significant sperm damage, inflammation, mortality, diarrhea, vomiting/contact dermatitis	dermal, reproductive, digestive	[11–14, 62]
			extract/oral	human/rat	with diarrhea, hypokalemia, pseudomelanosis coli, kidney failure as well as phototoxicity and hypersensitive reactions, carcinogenic reaction in rats	renal, digestive	[62]
		emodin only	extract/oral/0.7% aloin/200 mg/kg	mice	nonneoplastic lesions in the colon, intestinal tumors	digestive	[62]
MTCA [(1R,3S)-1-methyl-1,2,3,4-tetrahydro-[beta]-carboline-3-carboxylic acid]	Lepidium meyenii Walp/Brassicaceae Cabbage	root	powdered extract/oral	human	craving behavior, which is common in addictions, altered menstrual cycles, moodiness, cramps, gastritis, insomnia	hepatoxic, digestive, neurological	[69, 70]
		hypocotyls	500 mg hard gel capsules gelatinized powder/oral/2.0–3.5 g/day 1–3 months	human	Budd-Chiari syndrome, attention disturbances, weight loss, agitation, abdominal pain, epistaxis, gingival bleeding, headache, nausea, vomiting, abnormal liver function and estrogen functions such as endometriosis and breast cancer	digestive, reproductive, nervous system	[70]
Possibly ar-turmerone, α-turmerone and β-turmerone	Curcuma longa L./Zingiberaceae	turmeric essential oil	oral/2.8 mg/kg/d/66%	rat	elevations in serum alanine aminotransferase (ALT)	hepatotoxic, circulatory	[40]
Cyanogen glycosides	Sambucus nigra L./Adoxaceae	leaves, bark, stems, unripe berries	juice concentrate or juice (aqueous) extract/oral/11–12 g daily 4–5 days, OR 4 tablespoons a day	human	acute toxicity events, including reported nausea, vomiting, abdominal cramps, plus weakness, dizziness and numbness; stupor	digestive, neurological	[68]
	Withania somnifera (L.) Dunal/Solanaceae nightshade	whole plant	WS 250 mg and 500 mg capsules (Rx) (aqueous extract, 8:1) daily/oral/750 mg/day for 3 days	human	increased appetite, libido, and hallucinogenic effects with vertigo	neurological	[41]
		aqueous extract	platform combination-based formulations/oral/330–440 mg daily for 6 weeks/10.80%	human	Mild gut-related (mostly epigastric burning) AE was reported. A mild increase in liver enzymes [serum glutamic pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT)]	digestive, hepatoxic	[41]
TEG		aqueous extract		human/mice/rats	accidental consumption of high concentration TEG resulted in coma and metabolic acidosis.	hematological/nervous system/fetalogical	[78]

*Information was obtained directly from the sources cited in the manuscript, and the source in the manuscript corresponds to that in the table. Pertinent information on all compounds (organized alphabetically) are provided

▶ **Table 3** Common toxicity reports across the botanical supplement market in the US**.

Compound name and structure	Plant name/family	Plant part	Sample type/route of administration/dosage/% of constituents	Test organism	Side effects presented	Toxicity category	Ref.
Aconitine	*Aconitum carmichaeli* Debx./Ranunculaceae	prepared main root and lateral root	root is "prepared" (processed by boiling herb for several hours); poisoning has occurred when the dried herb was consumed or the herb was not boiled long enough; overdose/oral/lethal dose in humans is between 3–6 mg; reports of severe poisoning from 0.2 mg to 6 g (pure aconitine)	case study	poisoning, nausea, vomiting, numbness, irregular heartbeat, cold extremities	cardiovascular	[48]
	Aconitum pendulum N. Busch/Ranunculaceae		taken as raw plant or used in medicinal wine/oral/estimated lethal dose is 2 mg (pure aconitine); 1 g of the raw aconite plant or 5 mL of medicinal wine	case study	heart arrest due to its effects on voltage-gated sodium channels	cardiovascular	[48]
Aristolochic acid I	*Aristolochia fangchi* Y.C. Wu ex L.D.Chow & S.M. Hwang/Aristolochiaceae	root extract	combination of aristolochic acid I and II/oral/150–300 mg kg-1/77% AAI	rat/mice	renal effects: severe proximal tubule (PT) cells necrosis	renal	[84]
			combination of aristolochic acid I and II/oral/0.2; 1.0; 5.0, or 25 mg kg-1 day-1 for 28 days/77% AAI	rat/mice	renal effects: proteinuria and glucosuria. PT cells atypia, mild necrosis at highest dosage	renal	[81–83]
			combination of aristolochic acid I and II/oral/10, 50, or 100 mg kg-1 once/77% AAI	rat	renal effects: at 100 mg, proteinuria, mitosis, and necrosis of PT	renal	[81–83]
			combination of aristolochic acid I and II/oral/2.5 mg kg-1 day-1, 5 days a week for 14 days/55% AAI	rat	renal effects: glucosuria, proteinuria, proximal tubule injury, mononuclear cells infiltration, interstitial fibrosis	renal	[81–83]
			combination of aristolochic acid I and II/oral/0.1 mg kg-1 day-1, 5 days a week for 17–21 months/44% AAI	mice	renal effects: glucosuria and low molecular weight proteinuria; renal hypocellular interstitial fibrosis	renal	[81–83]
Aristolochic acid II	*Aristolochia fangchi* Y.C. Wu ex L.D.Chow & S.M. Hwang/Aristolochiaceae	root extract	oral/10, 50, or 100 mg kg-1 once/21% AAII	rat	renal effects: at 100 mg, proteinuria, mitosis, and necrosis of PT	renal	[81–83]
			oral/2.5 mg kg-1 day-1, 5 days a week for 14 days/45% AAII	rat	renal effects: glucosuria, proteinuria, proximal tubule injury, mononuclear cells infiltration, and interstitial fibrosis	renal	[81–83]
			dried flowers and brewed into tea/oral/max limit of daily intake set at 3 mg/person (max duration is 2 weeks)	case study	seizures, neurotoxicity	nervous system	[57]
Caffeine	*Paullinia cupana* Kunth/Sapindaceae		oral/200 mg overnight while fasting	case study	high blood pressure and slowed metabolic clearance with oral contraceptives	cardiovascular	[60]
			oral/2.5–7% caffeine/200 mg/dose, as much as 1800 mg	case study		nervous system	[75]
Cathinone	*Catha edulis Forsk*/Celastraceae	leaves	fresh khat leaves/oral/lethal dose/21 mg/kg and 51 mg/kg	human participant study and urine analysis	elevated liver enzymes and aminotransferase levels	hepatic	[34]
		fresh leaves	oral/1 week of daily use of 400 g	human	inhibits human CYP2D6 enzyme activity and marginal effect on CYP3A4	hepatic	[34]

cont.

▶ Table 3 Continued

Compound name and structure	Plant name/family	Plant part	Sample type/route of administration/dosage/% of constituents	Test organism	Side effects presented	Toxicity category	Ref.
Caulosaponin	Caulophyllum thalictroides (L.) Michaux/ Berberidaceae		oral/9.5 g/kg	rat	increased activity, ataxia, and clonic seizures	nervous system	[72]
Chelidonine	Chelidonium majus L/ Papaveraceae		oral	case studies	hepatitis	hepatic	[27–29]
Digitoxigenin	Nerium oleander L., N. indicum L., and N. odorum L./Apocynaceae	leaves	10–20 leaves; estimated oleander leaf dose to be 4 g	case study; 21 y.o. female	confusion, flushing, diarrhea, and hypokalemia	circulatory	[52–54]
Emodin	Aloe barbadensis Miller, Frangula alnus Miller/Asphodelaceae	nondecolorized whole leaf extract	whole nondecolorized extract/oral/given either 0, 500, 1000, 1500 ppm extract (in drinking water)/emodin content: 70.5 ± 4.5 µg/g	rat	dose-related increase in mucosal hyperplasia in large intestine, nonneoplastic lesions in large intestine and mesenteric lymph nodes	digestive	[62]
		pure emodin	40 and 80 µM for 24 h	mice	30–45% decreased hepatocyte viability	hepatic	[11]
		aloe vera leaf powder	oral/500 mg over 2–3 days for 5 years; 34.4 mg in Senna genus	case studies	acute toxic hepatitis; elevated liver enzyme concentrations; seizures, nephritis, gastrointestinal hemorrhage, and dyspnea.	hepatic	[12–15]
		nondecolorized whole leaf extract	oral/100 mg/kg	case studies	vomiting and diarrhea	digestive	[31,63]
	Frangula alnus Mill./ Rhamnaceae	bark extract	pure emodin extract/30 µm		significant apoptosis	not specified cell death	
Ephedrine	Ephedra sinica Stapf./ Ephedraceae	Ripped Force	18-oz. drink/oral/20 mg of ephedra alkaloids, along with 100 mg of caffeine, 250 mg of l-carnitine, and 240 µg of chromium, 2–3 times/day	case study	cardiac arrest	cardiovascular	[47]
		Ripped Force	18-oz. drink/oral/one capsule contains 10 mg of ephedrine and 100 mg of caffeine	case study	cardiac arrest, resulting in death	cardiovascular	[47]
		Ultimate Orange	capsules/oral/415 mg ephedrine + caffeine	case study	hemorrhagic stroke	cardiovascular	[47]
		Shape-Fast Plus	12 mg capsule/40 mg caffeine 3 times daily	case study	subarachnoid hemorrhage	cardiovascular	[47]
Estragole	Foeniculum vulgare Mill./Apiaceae		not specified/MO < 10, 1.9–15.8 mg per day	mice, rat	hepatomas	hepatic	[42–44]
Flavocoxid (combination of baicalin and catechins)	baicalin from Scutellaria baicalensis Georgi/ Lamiaceae	Limbrel	Limbrel/250–500 mg twice daily	human	bilirubin and liver enzymes become elevated	hepatic	[33]
		extract	oral/5 g/kg for 8 weeks	dog	loose stool, diarrhea, discomfort	digestive	[65]
	catechins from Acacia catechu (L.f.) Willd.,/Leguminosae		Limbrel/250–500 mg twice daily	human	bilirubin and liver enzymes become elevated	hepatic	[33]

cont.

▶ **Table 3** *Continued*

Compound name and structure	Plant name/family	Plant part	Sample type/route of administration/dosage/% of constituents	Test organism	Side effects presented	Toxicity category	Ref.
Folinerin	*Nerium oleander* L., *N. indicum* L., and *N. odorum* L./Apocynaceae	leaves	10–20 leaves; estimated oleander leaf dose to be 4 g	case study; 21 y. o. female	confusion, flushing, diarrhea, and hypokalemia	circulatory	[52–54]
Helenalin	*Arnica montana* L./Compositae	dried flower	Absinthii herba/oral/5 mg/person (max duration is 2 weeks)	human clinical trials	tachycardia, watery emesis, and epigastric tenderness	cardiovascular	[59]
Linamarin	*Manihot esculenta* Crantz/Euphorbiaceae	root	centrifuged cassava juice/expected to release 10–8 mg HCN/kg cooked food/given 100 g diet/kg body weight of gari	dog	generalized congestion and hemorrhage, peri-portal vacuolation of liver, swelling, vacuolation and rupture of epithelial cells of the PCT of kidney, myocardial degeneration and adrenal gland degeneration; in testes, there were occasional abnormal germ cells in the seminiferous tubules	hepatic	[37]
			intraesophageally/doses of 0.075–0.3 mg of linamarin/2 mL of cassava juice after 14 days	rat	behavioral and locomotion deficiencies	nervous system	[77]
Lobeline	*Lobelia inflata* L./Campanulaceae	leaves and seeds	oral/8 mg/"usually present in amounts of 1.0 mg per unit dosage form"	human case studies	nausea and epigastric pain	digestive	[66]
Menthofuran	*Mentha pulegium* L. or *Hedeoma pulegioides* L./Labiatae		pennyroyal essential oil/oral/10 mL or less	rat	produces gastritis	digestive	[31]
			oral/15 mL or more	case studies	can lead to death	hepatic	[31]
			oral/30 mL or more	case studies	known to cause chemical hepatitis, leading to liver dysfunction, renal failure, seizures, and death	hepatic	[31]
			pennyroyal essential oil/oral/250 mg/kg for 3 days	rat	hepatotoxicity	hepatic	[30]
Menthol	*Mentha piperita* L./Lamiaceae	peppermint leaf essential oil	essential oil/oral/over 40 drops	case study	chemical burn of oral cavity and pharynx with tachycardia, tachypnea, and edema of the lips, tongue, and uvula	dermal	[79]
N-methyltyramine	*Citrus aurantium* L./Rutaceae		Bitter Orange extract/oral/300 mg produced an acute myocardial infarction/varies from 1% to 30% in products/386 ppm of cyanogenic glycosides	case study	vasoconstriction and spasms in the coronary arteries, increasing heart rate and blood pressure	cardiovascular	[58]
Neriine	*Nerium oleander* L., *N. indicum* L., and *N. odorum* L./Apocynaceae	leaves	10–20 leaves; estimated oleander leaf dose to be 4 g	case study; 21 y. o. female	confusion, flushing, diarrhea, and hypokalemia	circulatory	[52–54]

cont.

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▶ **Table 3** *Continued*

Compound name and structure	Plant name/family	Plant part	Sample type/route of administration/dosage/% of constituents	Test organism	Side effects presented	Toxicity category	Ref.
Nordihydro-guaiaretic acid (NDGA)	*Larrea tridentata* (Sessé & Moç, ex DC.) Coville/ Zygophyllaceae	leaf	oral/LD: 0.8 g/kg/2%	guinea pig	renal lesions observed after 3 weeks	renal	[25]
			oral/4% of extract	rat	growth retardation, irritability, aggressiveness, hypoplasia of testicles and accessory sex glands	reproductive	[25]
			hydroethanolic extract of chapparal/oral 0.5 or 1% of compound (for 74 wks)	hamster	cysts of mesenteric lymph nodes developed	digestive	[25]
			NDGA compound only/oral/0.5% (for 2 yrs)	rat	growth inhibition observed after 6 mo, inflammatory cecal lesion and cyst enlargement after 2 yrs	digestive	[25]
		leaf	oral/0.3–6 g daily		toxic liver damage, jaundice	hepatic	[25]
Oleandrin	*Nerium oleander* L., *N. indicum* L., and *N. odorum* L./Apocynaceae	leaves	10–20 leaves; estimated oleander leaf dose to be 4 g	case study; 21 y. o. female	confusion, flushing, diarrhea, and hypokalemia	circulatory	[52–54]
Riddelliine/ symphytine	*Symphytum officinale* L. Also present in: *Ligularia dentata* (A. Gray)	leaf and root	oral/10 mg/kg (5 days a week for 13 wks)/oral/ 8, 16, or 33% (for 600 days) or 33% comfrey diet (for 480 days)	mice	liver tumors	hepatic	[19, 23]
	H. Hara, *Senecio scandens* Buch.-Ham., *Lithospermum erythrorhizon* Zicca Siebold & Zucc., *Onosma paniculatum* Bureau & Franchet/Boraginaceae	herb tea, comfrey pills	10 cups tea + additional pills (no quantity given)	female case study	hepatic veno-occlusive disease	hepatic	[21, 23]
Safrole	*Sassafras albidum* (Nutt.) Nees/Lauraceae	root	oral/fed oil as 0.117% of diet or safrole as 0.039% of diet for 2 years (68 yrs of human exposure)	rat	hepatocarcinomas, changes in kidneys, adrenals, thyroid, pituitary, and testes or ovaries	hepatic	[39]
Synephrine	*Citrus aurantium* L.		Bitter Orange extract/oral/300 mg produced an acute myocardial infarction	case study	increases blood pressure by increasing norepinephrine release	cardiovascular	[58]
Thujone	*Artemisia absinthium* L./ Compositae, *Salvia officinalis* L./Lamiaceae	leaf	sage leaf preparation/oral/15 mg	human clinical trials	facial redness, pupil dilation, increased heart rate, hallucinations, dry mouth, agitation	unsure how to specify	[71]
		leaf	25 or 50 mg/kg for 13 weeks, LD 2600 mg/kg	rats	seizures were observed		[71]
Usnic acid	*Usnea barbata* (L.) F. H. Wigg/Parmeliaceae	usnic acid compound	oral/100–200 mg of usnic acid taken daily for 2 weeks	mice and rat	liver failure	hepatic	[24]
		usnic acid compound	oral/500 mg of usnic acid taken daily for 2 weeks	case studies	liver failure	hepatic	[24]
Yohimbine	*Pausinystalia johimbe* (K. Schum.) Pierre ex Beille/Rubiaceae	bark	prescription drug yohimbine hydrochloride/oral/ LD: doses over 43 mg	human clinical trials	increased mean arterial pressure and heart rate	cardiovascular	[57]
		yohimbine compound	oral/5 to 15 mg	human clinical trials	elicitation of manic symptoms in bipolar disorder patients, lupus-like syndrome, and bronchospasm	circulatory	[57]

** Information was obtained directly from the sources cited in the manuscript, and the source in the manuscript corresponds to that in the table. Pertinent information on all compounds (organized alphabetically) are provided

enzyme activity *in vitro*, but when consumed by humans, ginkgo does not impact drug metabolism [18].

Pyrrolizidine alkaloids riddelliine and symphytine are compounds present in *Symphytum officinale*, commonly known as comfrey. This plant species is a member of the Boraginaceae family. When rats were orally given 10 mg/kg body weight for 5 days per week for 13 weeks, the animals experienced hepatopathy [19]. In one case study, a woman drank as much as 10 cups of comfrey herb tea in one day, along with taking comfrey pills, and developed hepatic veno-occlusive disease [20]. According to the U.S. National Library of Medicine's LiverTox database [21], cases of acute liver injury have been reported, usually beginning after 1 to 2 months of consuming comfrey. However, the database states comfrey hepatotoxicity is rare because consumption of comfrey is restricted or banned in many countries due to the knowledge of possible liver injury [21].

Pyrrolizidine alkaloids are also commonly found in the plants *Ligularia dentata, Senecio scandens, Lithospermum erythrorhizon*, and *Onosma paniculatum*. Because of the known liver toxicity demonstrated by these plants, pyrrolizidine alkaloids are banned in the USA and limited in Europe to 100 μg per day externally or 1 μg per day internally for no more than 6 weeks [22]. However, the European Medical Agency's Committee of Herbal Medical Products [23] recommends a daily intake of no more than 0.35 μg per day to avoid the risk of long-term toxicity affects.

Usnic acid is a dibenzofuran derivative present in *Usnea barbata* (L.) F.H. Wigg. of the Parmeliaceae family. Mice and rats were orally given 100 and 200 mg/kg body weight during a 2-week study. These animals experienced liver toxicity. Human case studies have shown that taking 500 mg of usnic acid for 2 weeks can induce liver failure [24].

NDGA is an antioxidant compound present in *Larrea tridentata* of the Zygophyllaceae family and is commonly known as creosote bush. Human case reports suggest that consuming 0.3–6 g daily of *L. tridentata* tablets can lead to toxic liver damage with jaundice. In guinea pigs, a lethal oral dose of NDGA is 0.8 g/kg body weight [25,26].

The isoquinoline alkaloid chelidonine is present in *Chelidonium majus* L. of the Papaveraceae family, also known as greater celandine. The presentation of hepatitis after celandine use has been mentioned in several human case studies [27–29].

Menthofuran is a compound present in pennyroyal oil, derived from *Mentha pulegium* or *Hedeoma pulegioides* of the family Labiatae. Rats were orally given 250 mg/kg of pennyroyal oil once daily for 3 days. These rats experienced hepatotoxicity [30]. Consumption of 30 mL or more of pennyroyal oil can cause hepatitis, leading to further liver dysfunction in humans [31].

Flavocoxid is a proprietary blend of baicalin and catechins. Baicalin is a compound from *Scutellaria baicalensis* (Lamiaceae) and the catechins are from *Acacia catechu* (Leguminosae). Baicalin has shown hepatoprotective activity in multiple animal and *in vitro* experiments [32]. EGCG is present in green tea extract, and it is believed that EGCG is responsible for hepatotoxicity attributed to green tea extract. EGCG is also present in flavocoxid, and researchers infer this catechin is responsible for liver injury caused by flavocoxid as well [32]. Limbrel is a flavocoxid commercial product derived from the bioflavonoids baicalin and catechins

that have been ground into tablets. When humans orally consume 250–500 mg of Limbrel twice daily, bilirubin and liver enzymes become elevated [32].

When human participants orally consumed 400 g of *Catha edulis* (khat) leaves (of the Celastraceae family) daily for a week (a dose demonstrative of frequent use of the leaves as a supplement), studies showed decreased activity of CYP2D6, a liver enzyme involved in metabolism [33]. The stimulant cathinone is a monoamine alkaloid present in the leaves of khat. In other case reports, toxic effects of khat use appear years later with elevated liver enzymes and aminotransferase levels, indicating the presence of liver damage [34]. An Australian case report [34] suggests that khat-associated hepatitis may be due to an autoimmune response. Khat is native to East Africa, and according to one paper [35], no khat-induced hepatitis has been reported. The toxicity may be the result of contaminants used to preserve khat during exportation, or hepatitis may be caused by individual abuse of drugs and alcohol [35]. Notably, the legal restriction on khat distribution commercially in the USA may limit its use by the public consumer [36]; however, improvised preparations and its use elsewhere highlight it as a supplement for investigation in this review.

Linamarin is a cyanogenic glucoside present in *Manihat esculenta* (Euphorbiaceae), known as cassava. The plant is often consumed in the West African food known as gari. Dogs were given 100 g/kg of gari over 14 weeks and liver vacuolation was observed in the test subjects [37]. Cassava is known as a cause of nonalcoholic chronic pancreatic disease in developing nations [38].

Safrole, an alkenylbenzene, is a phenylpropene present in *Sassafras albidum* (Lauraceae), commonly known as sassafras, and *Foeniculum vulgare*, commonly known as fennel. This plant has been used by the public primarily through sassafras essential oil. In one study, rats consumed sassafras oil as 0.117% of their diet or safrole as 0.039% of their diet for 2 years. Researchers calculated this would be the equivalent to humans consuming sassafras oil/safrole for 68 years. Among many adverse effects observed, hepatocarcinomas developed on the test subjects [39].

Alpha- and beta-turmerones are active compounds present in the essential oil of *C. longa* (Zingiberaceae), commonly called turmeric. In a rat model study, oral administration of 2.8 mg/kg per day resulted in elevated serum ALT in the liver, indicating the presence of liver damage [40].

W. somnifera, commonly known as ashwagandha and a member of the nightshade family, is commonly used as an herbal supplement in Ayurvedic medicine. In one clinical study, consumption of 330–440 mg a day for 6 weeks resulted in mild epigastric burning, as well as an increase in liver enzymes (SGPT and SGOT), indicating hepatic distress [41].

Estragole is an alkenylbenzene derived from *F. vulgare*, commonly known as fennel, of the Apiaceae family. Estragole has been known to induce hepatomas in rodents at high doses. These tumors are caused by the bioactivation by cytochrome P450s and sulfotransferases, giving rise to the ultimate carcinogenic metabolite 1′-sulfooxyestragole, which forms DNA adducts [42]. Indeed, *in vitro* studies of growing cell lines of human hepatomas have determined that activation of CYP1A2 and CYP2A6 enzymes ultimately lead to the formation of 1′-sulfooxyestragole, which is un-

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stable in aqueous environment and whose carbocation formed in solution reacts easily with DNA in the liver [43]. The margin of exposure of alkenylbenzenes such as estragole and safrole to cytotoxicity due to fennel consumption was calculated at 1.9–15.8 mg per day to be less than 10, meaning that daily intake was enough to cause genotoxicity and carcinogenic events in experimental animals, indicating the risk to human health and priority for risk management [43, 44].

Plants and plant constituents associated with cardiovascular toxicity

The literature has indicated that 12 compounds are known to exhibit cardiovascular toxicity. These compounds belong to 12 plant species and 9 families.

Ephedrine is an alkaloid with a phenethylamine skeleton found in various plants within the genus *Ephedra* (Ephedraceae). Ephedrine is a bronchodilator used to prevent low blood pressure during spinal anesthesia. Ephedrine is also found in dietary supplements that promote short-term weight loss, but those are now illegal in the USA. However, in traditional Chinese medicines that contains ephedrine (ma-huang), it is legal.

The ephedrine quantity in dietary supplements taken orally is about 20 mg per serving, and doses are taken up to two to three times per day. It has been shown that labels of dietary supplements do not list ephedrine content, or incorrectly report the amount of ephedrine in these products [45].

Ephedrine has been associated with cardiovascular dysfunction such as myocardial infarction, severe hypertension, myocarditis, and lethal cardiac arrhythmias [46]. The typical dose of ephedrine used for bronchodilation is 25–50 mg, but ephedrine doses associated with adverse events were less than this amount.

Four selected case studies were featured in the Haller and Benowitz paper [47]. One patient consumed a dietary supplement (Shape-Fast Plus) for 1 week and suffered a subarachnoid hemorrhage. Shape-Fast Plus was taken as a capsule three times a day before meals for weight loss. Each capsule contained 12 mg of ephedra alkaloids, along with 40 mg of caffeine. Another patient suffered a hemorrhagic stroke 90 min after consuming Ultimate Orange, a drink containing 415 mg of ephedra alkaloids and caffeine. This patient had also run 3 miles before the hemorrhagic stroke occurred. The last two cases feature a dietary supplement known as Ripped Force. Both patients went into cardiac arrest. The first patient was on asthma medications (albuterol and theophylline) and had consumed an 18-oz. bottle of Ripped Force before cardiac arrest occurred. The patient was drinking up to three Ripped Force bottles a day for an undisclosed amount of time. Each 18-oz. drink contained 20 mg of ephedra alkaloids, 100 mg of caffeine, 250 mg of L-carnitine, and 240 µg of chromium. The interaction of the theophylline and albuterol medications with the caffeine and ephedra in Ripped Force caused an arrhythmia that induced cardiac arrest. The next patient had taken two Ripped Force capsules each morning for 1 year. Each capsule contains 10 mg of ephedrine and 100 mg of caffeine. After a 20-min jog and consuming Ripped Force capsules for 1 year, this patient collapsed suffering a cardiac arrest, resulting in death. A case study by Haller and Benowitz indicates that caffeine "enhances the cardiovascular and central nervous system effects of ephedrine" [47].

Aconitine is a toxic compound found in the genus *Aconitum* (Ranunculaceae). *Aconitum carmichaeli* Debx. is a plant commonly used in traditional Chinese medicine. The prepared main root is called *chuan wu*, and *fu zi* is the prepared lateral root. These roots are prepared by boiling this herb for several hours. Poisoning has occurred when either the unprepared dried herb was consumed, herbs were boiled for an insufficient amount of time, or patients overdosed [48]. The lethal oral dose of *A. carmichaeli* prepared roots for humans is estimated to be 3–6 mg. However, severe poisoning has been reported after consuming anywhere from 0.2 mg to 6 g orally. Poisoning symptoms include nausea, vomiting, numbness, irregular heartbeat, and cold extremities [48]. *Aconitum pendulum* Busch is a plant that is consumed either as a raw plant or contained in medicinal wine. The estimated human lethal dose of the raw aconite plant is 1 g or 5 mL of medicinal wine. Overdoses related to this plant induced heart arrest due to its effect on voltage-gated sodium channels. The changes in sodium channels have been linked to aconitine [48]. Furthermore, aconitine has been known to inhibit the binding of acetylcholine and epinephrine to cholinergic and adrenergic receptors, respectively, in cardiac muscle cells, which may contribute to arrhythmic heart contraction [49].

Strychnine is a toxic, crystalline alkaloid that is most commonly found in the seeds of *Strychnos nux-vomica* L. (Loganiaceae). Strychnine causes its toxicity by interfering "with post-synaptic inhibition mediated by glycine in the brain and spinal cord" [50]. Although strychnine is an ingredient in rodent poison, it is also used in Tibetan medicine and Chinese folk medicine. If 30–120 mg of strychnine are consumed, it can be deadly toxic. In certain instances, children have consumed less than 10 mg and adults have consumed less than 16 mg, resulting in fatalities [50]. In one fatal case study, a patient ingested taupicine, a mole poison that was 10% strychnine. The blood sample from the patient contained 0.29 µg/mL of strychnine [51]. In another case, a patient ingested three teaspoons of strychnine (along with 15 mg of methocarbamol), and 0.8 mg/L of strychnine was found in the patient's blood sample. After ingesting strychnine, the patient exhibited tachycardia, hypertension, and intense muscle spasms [51].

Neriine, oleandrin, folinerin, and digitoxigenin are cardiac glycosides found in a number of plants that are commonly known as oleander, including *Nerium oleander, Nerium indicum*, and *Nerium odorum* (Apocynaceae). These cardiac glycosides are found in all parts of the plant. A 21-year-old female consumed 10–20 *N. oleander* leaves, resulting in confusion, flushing, diarrhea, and hypokalemia. The treating physicians estimated the lethal dose of oleander leaves to be 4 g. They formulated this estimation from the assumed volume of distribution of the glycosides in oleander leaves (1 L/kg) and the calculated lethal dose absorbed by their patient [52, 53]. Case studies with similar results have been reported [52–54].

These cardiac glycosides work by inhibiting Na^+/K^+ ATPase pumps, causing an accumulation of intracellular sodium in myocytes. This increase in intracellular sodium inhibits the exchange of sodium and calcium, resulting in an increase of intracellular cal-

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cium. The change in calcium concentration decreases the heart rate and enhances cardiac contraction. All of these changes can result in conduction block, ventricular arrhythmias, and asystole [55].

Through searching various databases, known toxic concentrations of the individual cardiac glycosides mentioned could not be identified. This may be due to the scant commercial availability of oleander to the consumer in USA markets. This is an area of research that warrants further investigation since various decoctions of oleander preparations are available online [56].

Yohimbine is an indole alkaloid that is found in the bark of the *Pausinystalia yohimbe* tree (Rubiaceae). Supplements containing yohimbine have been marketed as products that can improve sexual function, but certain dosages can increase or decrease systemic blood pressure. In human clinical trials of yohimbine hydrochloride, doses of 20 to 40 mg resulted in a moderate increase in blood pressure, and doses over 45 mg increased mean arterial pressure and heart rate. Yohimbine compounded was given in human and animal trials. After humans were given 5–15 mg, bipolar disorder patients exhibited manic symptoms, while other patients experienced lupus-like syndrome and bronchospasms. In animal studies with mice, the oral lethal dose was determined to be 43 mg/kg [57].

Citrus aurantium (Rutaceae) is the source of bitter orange extract. After the FDA banned ephedra from weight loss supplements, many manufacturers began using bitter orange extract and guarana as substitutes. Two of the active components in bitter orange extract are synephrine and N-methyltyramine. Synephrine is the main ingredient thought to enhance weight loss by suppressing appetite and boosting metabolism. Synephrine is also known to cause "vasoconstriction and spasms in the coronary arteries, increasing heart rate and blood pressure" [58]. The amount of synephrine in these products varies from 1% to 30%. Another active component, N-methyltyramine, increases blood pressure due to increasing norepinephrine release [58]. The combining effects of these two components may cause potential cardiotoxicity.

In a case study, one patient had orally consumed 300 mg of bitter orange extract daily and suffered an AMI. The treating physicians suspected bitter orange extract was the cause of it. Researchers advise that more evidence about the safety of this extract and its components be provided before these supplements are purchased over-the-counter [58].

Helenalin, is found in the *Arnica* genus. Helenalin, a sesquiterpene lactone, is a known toxin in *Arnica montana* (Compositae), which inhibits platelet aggregation. In one case study, a patient had dissolved dried flowers in oil and topically applied them to heal bruises. Then, the patient ingested the flowers in a cup of tea. Two hours after drinking the tea, the patient experienced tachycardia, watery emesis, and epigastric tenderness. After receiving intravenous fluids and antiemetics, the patient was stabilized [59].

Turmerones found in *C. longa* (Zingiberaceae), previously described for its hepatotoxic qualities, has also presented acute anemia when 2.6 mg/kg per day were administered orally to rats. Inadequate oxygenation in this case may, therefore, pose a keen circulatory risk in human cases [40].

Caffeine derived from *Paullinia cupana*, commonly known as guarana of the Sapindaceae family, is an ingredient commonly used in energy drinks and beverages. In a clinical trial, eight healthy adults received a single dose of 200 mg caffeine after an overnight fast. After plasma and urine samples were obtained, and heart rate and blood pressure were monitored for 14 h, it was found that blood pressure increased significantly to a maximum of 14 mmHg. In addition, metabolic clearance was slowed in those patients taking oral contraceptives, indicating that drug-botanical interactions could pose a greater risk for toxicity due to caffeine [60]. In one study, active fractions from dried guarana seed extract used in soft drinks were subject to liquid-chromatography mass-spectroscopy and analyzed for content. It was suggested that complexes containing caffeine and catechins (and their dimers) might be responsible for antiplatelet aggregatory activity, which may be causing such a drastic increase in blood pressure [61].

Plants and plant constituents associated with toxicity to the digestive system

Five plant compounds and eight plant species from seven plant families were found to cause toxicity events.

Menthofuran, a compound mentioned previously in this review as hepatotoxic, has also been found to induce adverse effects on the digestive system. *M. pulegium*, (Lamiaceae), naturally produces menthofuran. Menthofuran is found in many essential oils, including pennyroyal. Case studies have shown that ingesting 10 mL or less of pennyroyal oil can cause gastritis [31].

Emodin is another compound categorized as hepatotoxic, but has effects on the digestive system as well. This compound is found in *A. barbadensis* (Asphodelaceae), known as aloe vera. The National Toxicology Program conducted toxicity studies on various plant extracts. When rats were orally given aloe vera whole, nondecolorized extracts, a dose-related increase in mucosal hyperplasia in the large intestine occurred, while nonneoplastic lesions in the large intestine and mesenteric lymph nodes were also observed. The emodin content of the aloe whole leaf extract is estimated to be 70.5 µg/g. Researchers suggest the intestinal tumors developed due to the anthraquinone emodin being transformed into mutagenic components in the intestine. The recommended dose per day for humans is 0.43 mg/kg or about 10–30 mg/day [62]. According to the U.S. National Library of Medicine Toxicology Data Network, mild toxic overdoses of emodin can induce vomiting and diarrhea, but severe overdoses can result in gastrointestinal hemorrhage [15]. For example, in one experiment, oral administration of 100 mg/kg whole leaf aloe extract resulted in vomiting and diarrhea [63–64].

Scutellaria baicalensis, a member of the Lamiaceae family, is commonly known as Chinese skullcap. A 5 g/kg extract of Chinese skullcap was given to dogs over an 8-week period, and loose stool was observed as a result. Diarrhea and stomach discomfort have been observed in human case reports. Dose and preparation, unfortunately, were not reported [65].

NDGA is a compound that has been previously discussed in this paper for its hepatotoxic activity. When NDGA was isolated, it induced abnormalities in the gastrointestinal tract. Rats received an oral administration of NDGA extract for 74 weeks (0.5 or 1% of the

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extract was NDGA). After these administrations, mesenteric lymph node cysts developed in the test subjects. In another study, rats were given an extract (0.5% of the extract was NDGA) for 2 years. Following this time period, inflammatory cecal lesions and cyst enlargement occurred [25]. These findings correspond with reports of renal and hepatotoxicity in humans after long-term use of NDGA and its origin, *L. tridentata* [26].

Lobeline is an alkaloid found in *Lobelia inflata*, also known as "Indian tobacco". *L. inflata* is a member of the Campanulaceae family. Lobeline is found in the leaves and seeds of this plant. When commercially sold, lobeline is present in a 1-mg per unit dosage. When humans consume 8 mg of lobeline, nausea and epigastric pain was reported [66]. Lobeline has been known as a ligand for nicotinic acetylcholine receptors that competitively inhibits its acetylcholine binding to smooth muscle tissue to induce peristalsis [67].

Sambucus nigra, commonly known as European elderberry, comes from the Adoxaceae family. Elderberry leaves, bark, stems, and unripe berries are known to contain cyanogen glycosides, which commonly present toxic events in clinical cases and may present in Sambucol, a syrup product made from elderberry juice concentrate. Oral consumption in human cases at 11–12 g daily for 4–5 days, or 4 tablespoons a day, has resulted in reports of nausea, vomiting, abdominal cramps, weakness, dizziness, numbness, and stupor [68].

L. meyenii, commonly known as maca and is a member of the cabbage family, possess a root commonly ground or extracted for human consumption as a sexual and reproductive enhancing supplement. One active compound attributed to this altered sexual behavior and reported in toxicity and adverse events includes MTCA. Consumption of a powdered root extract containing MTCA has resulted in cramps and gastritis [69]. Furthermore, according to a literature review of clinical trials associated with maca, oral consumption of 2.0–3.5 g per day in the form of 500 mg hard gel powder extract tablets of maca primary leaves for 1 to 3 months resulted in weight loss, abdominal pain, nausea, and vomiting [70].

Plants and plant constituents associated with neurotoxicity

Six compounds from six species and six families were associated with neurotoxicity.

Thujone is a compound present in *Artemisia absinthium* (Compositae) and *Salvia officinalis* (Lamiaceae), commonly known as sage leaf. In 2012, the European Medicines Agency issued a statement about the safety of thujone in herbal medicinal products. The EMA concluded the maximum limit of daily oral intake for Absinthii herba was established at 3 mg/person and *S. officinalis* was limited to 5 mg/person. Both herbal products should only be used for 2 weeks maximum. The report assessed that low-dose exposure to thujone (3–7 mg/day) may be safe, but higher concentrations of thujone may pose a risk.

When rats consumed thujone in higher concentrations (concentrations of 25 or 50 and greater mg/kg for 13 weeks), seizures were observed. In other animal studies, rats were given various doses of sage essential oil. A lethal (oral) dose was determined to be 2600 mg/kg. When humans consume higher doses (15 mg), subtle changes in attention and mood were observed [71].

Caulosaponin is present in blue cohosh, *Caulophyllum thalictroides* (Berberidaceae). This compound has been isolated and a lethal dose has been determined. In neonates born to women who have taken blue cohosh, perinatal stroke, acute myocardial infarction, congestive heart failure, multiple organ injury, and neonatal shock have occurred. After orally consuming blue cohosh, patients experienced side effects including diarrhea, increased levels of blood pressure and blood glucose, and stomach cramps. These adverse events are believed to be caused by the toxic alkaloid methylcytisine [72, 73]. A biochemical study of the constituents in blue cohosh revealed that all studied dietary supplements of blue cohosh contain N-methylcytisine [74].

The seeds and fruit of guarana (*P. cupana*, Sapindaceae) are often a source of caffeine for herbal supplements, as previously mentioned. In a case study, a weight loss supplement contained 2.5–7% caffeine (200 mg/dose). If patients choose to self-medicate and increase supplement usage, patients may consume as much as 1800 mg of caffeine [74]. The safety limit recommended by the FDA for daily caffeine consumption is only 400 mg, or the equivalent of four to five cups of coffee [75].

Linamarin, previously featured as a hepatotoxic compound of *Manihat esculenta* (Euphorbiaceae), has been associated with neurotoxicity in animals. In an animal study where cassava-fed animals were compared to control animals, cyanide-fed animals, and malnourished animals, researchers found motor coordination of the cassava-fed animals was similar to the other groups studied. However, the plasma thiocyanate concentration as well as urinary thiocyanate excretion and elevated urinary protein excretion for the cassava-fed animals differed from all other studied groups. Researchers concluded that neurotoxicity could be a result of linamarin [76]. Another study featuring Wistar rats corroborates these findings. After consuming doses of 0.075–0.3 mg of linamarin in 2 milliliters of cassava juice for 2 weeks, the test subjects experienced behavioral and locomotion deficiencies [77].

L. meyenii, or maca, has been previously mentioned for its digestive toxicity. Human consumption of the root extract has also been associated with a significant impact on neurological functions, resulting in side effects that include craving behavior, moodiness, and insomnia [69]. Consumption of the primary leaf extract in the form of hard gel powder extract tablets at 2.5–3.0 g/day for 1 to 3 months has also produced reports of headaches, attention disturbances, and agitation [70].

W. somnifera (nightshade), previously mentioned for its hepatotoxic properties, contains the active compound TEG, which at accidental high concentrations in humans has resulted in coma and metabolic acidosis [78]. Similar neurological toxicity has also resulted upon oral administration to both mouse and rat models (5630 mg/kg/day in rats and 563 mg/kg/day in mice) [79]. Furthermore, human consumption of 250 mg and 500 mg 8 : 1 aqueous extract *W. somnifera* tablets at 750 mg/day for 3 days has resulted in the adverse events of increased appetite, libido, and hallucinogenic effects with vertigo [80].

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Plants and plant constituents associated with renal toxicity

Aristolochic acids I and II are found in *Aristolochia fangchi*, a member of the Aristolochiaceae family. Various animal studies presented in ▸ **Table 3** studied varying concentrations of each aristolochic acid and its effect on the body. Low doses produced proteinuria and glucosuria, while an increasing dosage produced necrosis and interstitial fibrosis [81–83]. In a 1992 human study, over 50 % of patients experienced Belgian epidemic-nephropathy upper urothelial cancer due to long-term consumption of a weight loss pill. ESRD was also observed in 70 % of aristolochic acid-poisoned patients, as well as hypertension, proteinuria, and glycosuria [82]. In 1996 case studies, aristolochic acid nephropathy was directly correlated to Chinese herb nephropathy. Women (age range from 27–42) consumed Chinese herbal weight loss pills for 13–23 months. Renal transplantation was necessary 9–27 months after the women stopped taking these pills. Patients in these case studies experienced renal and urinary tract degradation symptoms [83].

In another literature review of herbal medicine toxicities, aristolochic acid nephropathies such as Fanconi syndrome, renal failure, and tubular necrosis were observed in patients from Taiwan, Japan, and China [84]. Molecular analysis revealed that aristolochic acid is responsible for covalently binding to DNA in the nucleus, forming AL-DNA adducts that cause mutation or transcription error in protein synthesis that may cause these renal issues, particularly in cases of renal cell carcinoma [85]. Safrole is a compound present in sassafras and fennel essential oil that has been previously discussed as hepatotoxic but also has effects on the kidney. Many systemic effects were observed after two different groups of rats were administered either sassafras oil or safrole for 2 years. Oil comprised 0.117 % of the diet in one group, while subjects in the second group were given pure safrole, which constituted 0.039 % of their diet. Changes in kidney structure were noted postmortem [39].

Emodin, a toxic anthraquinone present in whole leaf *A. barbadensis* extract, has also demonstrated evidence for renal toxicity in rat models. In one study, the whole leaf extract administered orally to rats resulted in hypokalemia and renal failure [62].

Plants and plant constituents associated with reproductive toxicity and developmental effects

NDGA is a compound that has effects on the digestive and reproductive organ systems. NDGA is found in the leaves of chaparral (*L. tridentata*, Zygophyllaceae). A hydroethanolic extract of chaparral (4 % NDGA) was administered to hamsters. Numerous effects were observed, including growth retardation, irritability, aggressiveness, and hypoplasia of testicles and accessory sex glands [25].

Emodin, mentioned previously for its toxic effects in *A. barbadensis*, has also demonstrated reproductive toxicity in an animal study. In one rat model, oral administration of 100 mg/kg of whole leaf aloe extract produced reproductive inflammation and toxicity, notably, significant sperm damage [62].

L. meyenii, or maca, has been previously mentioned for its digestive and neurological toxicity. MTCA, an active ingredient in the maca root, has also been associated with causing reproductive distress in the form of altered menstrual cycles [65]. According to a literature review on clinical trials conducted involving maca, oral consumption of maca at 2.0–3.5 g/day for 1 to 3 months has resulted in adverse side effects of abdominal pain, gingival bleeding, and abnormal functioning of estrogen-dependent systems, such as endometriosis and breast cancer [26].

Plants and plant constituents associated with toxicity of the endocrine system

Safrole has been reported as hepatotoxic and toxic to kidneys in a study where rats were administered sassafras essential oil (0.117 % of diet) or pure safrole (0.039 % of diet) for 2 years. Subjects were noted as also having changes to various endocrine organs, including adrenals, thyroid, pituitary, and testes or ovaries [39].

Plants and plant constituents associated with dermal toxicity

Menthol is a well-known compound present in the *Mentha* genus of the Lamiaceae family. *Mentha piperita* (peppermint) is the origin of peppermint leaf essential oil. In a case study, a patient ingested over 40 drops of peppermint leaf oil, afterwards experiencing a chemical burn of the oral cavity and pharynx. The patient also showed tachycardia, tachypnea, and edema of the lips, tongue, and uvula [79].

Discussion

In conclusion, based on the case studies and experiments previously mentioned, there is an overwhelmingly vast degree to which HDSs may induce toxicity events to multiple body systems in both animals and humans. A total of 47 known compounds in 55 different plant species from 46 plant families demonstrated harmful side effects due to hepatotoxicity, cardiovascular toxicity, central nervous system toxicity, and digestive system toxicity. These studies provide relevant evidence to both the FDA and to the public consumer for the growing need of awareness of the degree of toxicity in HDSs. Furthermore, the accumulation of these studies speaks to an immediate need to hold manufacturers of these substances accountable for ensuring that the products they manufacture and release to the market do not pose a threat to public health. Moreover, this evidence speaks to the necessity for further *in vitro* bioassay, animal experimentation, and clinical investigation that may shed further light on the possible toxicity of commonly used HDSs.

While 49 known toxic plant compounds have been observed in this literature review, the investigation into the toxicity of plant supplements still has ground to cover. While case studies often demonstrate the toxic effects of active plant compounds, there is very little information provided in the literature about the exact minimum toxic or lethal doses in animals and humans. In fact, many studies and sources report only toxicity and adverse events resulting from herbal supplements after consumption of doses many times higher than the therapeutic doses recommended by supplement manufacturers. Furthermore, a significant amount of the literature considered for this review only established cytotoxicity using *in vitro* models. Additional studies are needed in order to establish relevancy to humans. Moreover, it may be necessary

to initiate *in vitro* bioassays of other dietary supplement ingredients that may not show immediate adverse side effects, but are nonetheless very commonly used. These investigations may reveal as yet unknown toxicities or even advances in efficacy that these supplements may pose to public health that are unknown to manufacturers and/or the FDA. It is also prudent to consider that adverse events related to the consumption of botanical dietary supplements and other herbal medicinal drugs may be due to factors that cannot be easily identified by reading product labels for harmful plants or active ingredients. Adverse events may be related to several other factors, such as contamination with adulterants in the manufacturing process, ingredients benign by themselves that may react negatively with each other or other drugs, dosage variability, or the consumers themselves who may constitute special populations that may be at risk (i.e., children, pregnant women) [9]. These factors necessitate further inquiry and research to further understand the cause of adverse medical events connected to these products and mitigate prevention of such events in the future.

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Conflict of Interest

The authors declare no conflict of interest.

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