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Adverse Effects of Nutraceuticals and Dietary Supplements

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Abstract

Over 70% of Americans take some form of dietary supplement every day, and the supplement industry is currently big business, with a gross of over $28 billion. However, unlike either foods or drugs, supplements do not need to be registered or approved by the US Food and Drug Administration (FDA) prior to production or sales. Under the Dietary Supplement Health and Education Act of 1994, the FDA is restricted to adverse report monitoring postmarketing. Despite widespread consumption, there is limited evidence of health benefits related to nutraceutical or supplement use in well-nourished adults. In contrast, a small number of these products have the potential to produce significant toxicity. In addition, patients often do not disclose supplement use to their physicians. Therefore, the risk of adverse drug-supplement interactions is significant. An overview of the major supplement and nutraceutical classes is presented here, together with known toxic effects and the potential for drug interactions.

INTRODUCTION

Dietary supplements are products that are ingested in addition to the regular diet to provide additional health-promoting nutrients. In the United States, dietary supplements are defined and regulated according to the Dietary Supplement Health and Education Act (DSHEA) of 1994 (1). According to the DSHEA, a dietary supplement is a product that is intended to supplement the diet; contains dietary ingredients including vitamins, minerals, amino acids, herbs, and botanicals; is intended to be ingested as a pill, capsule, tablet, or liquid; and is labeled as being a dietary supplement (1, 2). Food items that are fortified with nutrients such as vitamins and minerals to ensure proper nutrient levels are not considered dietary supplements. The term nutraceutical is not defined by US law but is generally understood to refer to a purified product derived from a human food source and purported to provide extra health benefits beyond the basic nutritional value found in foods.

The US Food and Drug Administration (FDA) regulates dietary supplements in a markedly different way than it does regular drugs. A manufacturer of a drug needs to document its effectiveness and safety before it can be brought to the market. There is no requirement for demonstrating the efficacy of a dietary supplement for any health condition. Manufacturers of dietary supplements are not allowed to claim that the supplement can be used for treating or preventing any particular disease. However, statements pertaining to general well-being, function, and health can be allowed provided a disclaimer is listed on the product with the text, "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease" (2). The requirements for safety of dietary supplements are much less stringent than are those for a drug. No clinical trials are required. Ingredients sold in the United States before October 15, 1994, do not need safety evaluation by the FDA, as they are generally recognized as safe based on their historical use. For a new dietary ingredient not sold before October 15, 1994, the manufacturer must notify the FDA and provide reasonable evidence that it is safe for human consumption (2).

Dietary supplements are widely used. Half of adults in the United States report having used at least one supplement in the past 30 days (3). The most cited reasons for taking the supplements were to improve overall health, to maintain health, and, especially among women, for bone health. The most commonly used supplements were multivitamin and mineral supplements, calcium supplements, and omega-3 or fish oil (3). About a quarter of the supplements were used based on advice by health-care providers. Thus, most decisions to use supplements are made by the consumers themselves.

Despite their popularity, the health benefits of dietary supplements are questionable. Lack of vitamins will certainly cause deficiency diseases such as scurvy, beriberi, pellagra, and rickets. However, the vitamin content of normal well-balanced diets is sufficient to avoid these diseases. Studies aimed at determining effects of supplements often give conflicting results. There currently does not seem to be any scientific consensus on whether vitamins (4) or any other dietary supplements prevent disease or have health benefits in well-nourished individuals.

The intake of dietary supplements is generally safe but not totally without risk. This review is not intended to be a comprehensive report of all known adverse effects for all dietary supplements. Instead, we discuss adverse events for the most commonly used supplements, such as vitamins, minerals, omega-3 or fish oil, soy protein, and plant-derived antioxidant and anti-inflammatory nutraceuticals. We also discuss weight-loss, bodybuilding, and various botanical supplements that have been associated with more severe adverse effects.

Because dietary supplements can be brought to the market without the support of clinical trials, there is a paucity of systematic studies of adverse effects. Case reports of symptoms appearing after intake of a supplement often provide the first hint that there can be side effects associated with the supplement. However, it is close to impossible to show causation from a single case report.

The link can be strengthened if symptoms disappear with cessation of intake and reappear if the supplement is ingested again. Otherwise, an accumulation of cases over time or the appearance of a cluster of cases can ultimately establish that intake of a supplement can result in adverse effects.

VITAMIN AND MINERAL SUPPLEMENTS

By the early twentieth century, it had become clear that nutrition consisting solely of carbohydrates, fats, and proteins is insufficient for maintaining health. Casimir Funk coined the term "vitamine" in 1912 to describe the micronutrients whose deficiencies cause beriberi, scurvy, and pellagra (5). As the various vitamins were isolated and synthesized, a market for vitamins quickly developed. Today, multivitamin and multimineral, vitamin, and mineral supplements are the most widely used dietary supplements by the American population (3, 6). It has been reported that 33% of US adults use multivitamin and/or multimineral supplements (7) and that this is as high as 32–47% among male military personnel and 40–63% among military women (8). Among long-term cancer survivors, use of vitamin or mineral supplements is even higher, at 64–81% (7).

Although adequate intake of these micronutrients is required to maintain optimal health, the possibility of toxicity increases with increasing dose (9). Because dietary micronutrient deficiency is increasingly rare in developed counties, most supplement consumers actually have excess vitamin and mineral intake. Despite the widespread belief that vitamin and mineral supplements are beneficial to health, recent reviews of vitamin and mineral supplement trials in community-dwelling adults with no nutritional deficiencies have concluded that there is no clear evidence of beneficial health effects. These include primary or secondary prevention of chronic diseases including cardiovascular disease, cancer, and cognitive decline, as well as effects on overall mortality (10, 11). Indeed, there is evidence for possible harm from consumption of individual vitamins and mineral in excess. Toxicity following consumption of water-soluble vitamins is rare. However, photosensitivity and neurotoxicity have been reported at doses higher than 500 mg/day of pyridoxine (vitamin B6) (12), and cases of pyridoxine-associated chronic sensory polyneuropathy have been reported in elderly patients consuming multivitamin supplements (13). Reports of toxicity associated with overconsumption of supplemental antioxidant fat-soluble vitamins are more prevalent. Vitamin E is a family of eight related tocopherols and tocotrienols, of which α-tocopherol is the form generally used in supplements. Doses of 800–1,200 mg/day can result in bleeding associated with antiplatelet action, and doses above 1,200 mg/day can result in diarrhea, weakness, blurred vision, and gonadal dysfunction (12). Moreover, vitamin E supplementation following radiation therapy in a randomized trial of head and neck cancer patients was associated with increased cancer recurrence in the first 3.5 years of follow-up (14), and meta-analysis has suggested an increase in all-cause mortality after high-dose vitamin E supplementation (15). Toxicity has also been associated with consumption of supplemental vitamin A and its provitamin carotenoid precursors. In two large clinical trials, the Retinol Efficacy Trial (16) and the Alpha-Tocopherol, Beta Carotene Cancer Prevention (ATBC) Study (17), male smokers receiving β-carotene supplements had significantly increased the risk of lung cancer. The ATBC study further showed that prostate cancer incidence and mortality were increased in male alcohol users consuming the supplement. An additional two studies have suggested increased mortality in smokers consuming β-carotene supplements (18, 19). Excess vitamin A supplementation has been suggested to be associated with adverse effects on bone health, including low bone mineral density and increased fracture risk (20). In addition, women consuming large amounts of vitamin A supplements during pregnancy have been reported to have increased incidence of congenital abnormalities (21). There is also a case report of intrahepatic cholestasis in a patient with chronic hypervitaminosis A after 12 years of supplement consumption, which resolved after supplements were ceased (22). Toxicity can arise

from excess consumption of minerals as well as vitamins. In particular, there is an increased risk of hyperchromatosis, an iron storage disease associated with liver injury after excess consumption of iron or multimineral supplements (23, 24). This can be exacerbated by alcohol consumption (24).

FISH OIL AND OMEGA-3 FATTY ACIDS

Omega-3 fatty acids are essential fatty acids that cannot be synthesized de novo in humans and therefore must be provided through the diet (25). A link between fish oil and ischemic heart disease was suggested by a widely publicized study from 1971 of Eskimos (Greenlanders) from the west coast of Greenland (26). Greenlanders eating a traditional meat and fish diet rich in polyunsaturated omega-3 fatty acids had significantly lower levels of plasma total lipids, plasma cholesterol, plasma triglycerides, and pre β-lipoprotein (equaling very low density lipoprotein) than both Danes and Greenlanders living in Denmark. The authors hypothesized that this diet contributed to the low incidence of ischemic heart disease and diabetes among Greenlanders. Since then, polyunsaturated omega-3 fatty acids taken in the form of fish oils, krill oil, or mixtures of docosahexaenoic and eicosapentaenoic acids, also known as DHA and EPA, purified from fish oils have become widely used dietary supplements. These fatty acids have metabolites with anti-inflammatory properties and have electrical stabilizing effects on ion channels in cardiac myocytes (27, 28). They have been linked to anticancer and cardioprotective effects (29, 30). However, the therapeutic benefits on cardiovascular diseases are still controversial owing to disparate findings from different clinical trials (31).

It appears that fish oil and omega-3 fatty acids are well tolerated, even at doses of 1,000–2,000 mg/day, and there is little evidence of toxicity. However, simultaneous consumption of fish liver oils that also contain vitamin A and multivitamin supplements could result in hypervitaminosis A. Furthermore, fish oils and omega-3 fatty acid supplements may exacerbate anticoagulation and promote bleeding in patients taking anticoagulant medications such as warfarin (32, 33).

PROTEIN POWDERS AND INFANT FORMULA

Protein powders consisting of the dairy proteins casein and whey and of vegetable proteins in soy protein isolate (SPI) are popular supplements among athletes and body builders. These proteins are also the basis of infant formulas fed to over 4 million US infants each year. The dairy proteins appear to have little toxicity except in individuals with allergies to cow's milk protein, although excessive consumption may result in ketosis. In contrast, there is an ongoing debate with regard to the potential safety of SPI. This debate is related primarily to the presence of weakly estrogenic compounds—the isoflavones genistein and daidzein, which are among the 100 phytochemicals that remain bound to the protein isolate (34). These compounds can reach potentially estrogenic levels after SPI consumption in soy formula–fed infants and in children, men, and postmenopausal women taking soy protein supplements. Concerns have focused on potential estrogenic effects in early development resulting in reproductive toxicity, infertility, demasculinization, and increased promotion of estrogen-responsive cancers such as breast and endometrial cancer (35–37). Researchers have conducted several clinical studies of SPI and soy formula toxicity. Epigenome-wide DNA methylation analysis of vaginal cells from cow milk formula– and soy infant formula–fed girls indicated differential DNA methylation associated with decreased expression of the estrogen-responsive proline rich 5-like (*PRR5L*) gene (38). In addition, epidemiological studies have suggested a slightly earlier age of menarche (12.4 versus 12.8 years) and less female-typical play in soy formula-fed girls (39, 40). In contrast, data from a longitudinal ultrasound study of breastfed and cow milk formula– and soy formula–fed infants (the Beginnings

study) demonstrated no significant effects on testis or prostate volumes or structural characteristics at ages 1 year and 5 years (41, 42). In addition, a retrospective cross-sectional study of adults fed soy formula or cow-milk formula as infants did not find significant differences in responses to questions about health and reproduction (43). Moreover, in adult men, a recent meta-analysis showed no significant effects of soy protein on male reproductive hormones (44).

Animal studies of SPI and soy formula toxicity have likewise been contradictory. Akingbemi et al. (45) reported that perinatal exposure to diets made with soy resulted in suppressed steroidogenesis, decreased testosterone secretion, and increased Leydig cell proliferation in rats. Similarly, Sharpe and colleagues (46, 47) reported that marmoset monkeys fed soy infant formula had suppressed serum testosterone concentrations. Increased testis size and increased Leydig cell numbers per testis were also observed in these monkeys at adulthood, consistent with compensated Leydig cell failure. In adult female ovariectomized mice, feeding SPI increased growth of human breast cancer cell xenografts, consistent with an estrogenic effect (48). These studies, and concerns regarding estrogenicity, led to a recent review of the safety of soy infant formula by a panel from the Center for the Evaluation of Risks to Human Reproduction established by the National Toxicology Program and the National Institute of Environmental Health Sciences. However, the committee was unable to issue a conclusive recommendation regarding developmental and reproductive toxicity as a result of limitations in the available human data (49). In contrast to the small number of animal studies with SPI suggesting estrogenicity, lifetime feeding studies in rats fed with SPI, the sole protein source in soy formulas, revealed no effects on sex organ weights, serum sex steroids concentrations, or fertility (36). Moreover, chronic feeding studies with SPI in adult male cynomolgus macaque monkeys have also shown no effect on testis weight, morphology, serum testosterone or estradiol concentrations, or sperm counts (50). In addition, our laboratory has conducted a series of studies in ovariectomized adult female rats; prepubertal male and female rats; and neonatal piglets in which we have utilized genomics analysis, either with Affymetrix chips or RNA sequencing, to examine head-to-head gene expression profiles in the liver, bone, mammary gland, uterus, and testis after treatment with 17β-estradiol (E2) or feeding SPI (51–56). These studies revealed only minor overlap between E2 and SPI-regulated genes (3–10%) representing specific subsets of E2 regulated pathways, indicative of actions similar to those of selective estrogen receptor modulators, rather than weak estrogens, and with either no effect or antagonist actions on reproductive and proliferative pathways.

NUTRACEUTICALS

Most commonly used nutraceuticals are compounds derived from fruits and vegetables. They are often compounds with antioxidant or anti-inflammatory properties that are suggested to provide protection against chronic diseases such as cardiovascular disease, diabetes, cancer, and osteoporosis (57). Widely consumed nutraceuticals include flavonoid plant pigments such as anthocyanins from berries, flavonols from dark chocolate, polyphenols such as resveratrol from red grapes, catechins from tea, and quercetin. There are little data to suggest that these compounds are toxic. However, metabolites of epigallocatechin gallate—the active catechol in green tea extract, typically considered to be responsible for green tea's antioxidant properties—are suspected to enhance oxidative stress and have been associated with liver injury (58). It is also far from clear that consumption of these nutraceutical supplements has true health benefits, given a lack of large clinical trials (57). The most intensively studied nutraceutical flavonoids are the soy-derived isoflavones genistein and daidzein and the daidzein metabolite equol. Unlike other flavonoids, the isoflavones in their purified form have been shown to possess estrogenic properties in vitro and in animal models, including the ability to produce uterine hypertrophy or reproductive tract malformations,

reduce testis size, inhibit androgen production, reduce fertility, and stimulate estrogen-dependent tumor growth (36, 37, 45, 48, 49, 51, 52, 56). Since evidence emerged demonstrating health risks following hormone replacement therapy in postmenopausal women, menopausal women have increasingly turned to dietary supplements to treat symptoms such as hot flashes, depression, and bone loss. A recent survey indicated that as many as 42% of such women were using soy products, including isoflavone extracts and purified isoflavones such as genistein (58). Because these are concentrated or purified products, they can achieve far higher plasma levels than when isoflavones are consumed as part of SPI or soy foods, which are complex mixtures of bioactive proteins, peptides, and over one hundred phytochemicals (34, 36, 51). There have been case reports of endometriosis in women consuming isoflavone supplements (59), and, given the clear evidence of estrogenicity, there is a likelihood of increased risk of estrogen-sensitive cancers in consumers of these products.

WEIGHT-LOSS, SPORTS, AND BODYBUILDING SUPPLEMENTS

As more and more of the world's population becomes overweight and obese, there is a huge market for weight-loss products, including dietary supplements. Military service members, athletes, and bodybuilders also commonly ingest dietary sports supplements intended to burn fat and increase performance, muscle mass, or strength. As examples, 53% of active-duty US Army soldiers reported using at least one dietary supplement per week (60), and 64% of college students participating in athletics used dietary supplements to enhance performance (61). The supplements are often proprietary blends of several supposedly natural ingredients. They are not without risk of adverse effects. A recent review estimated that the proportion of drug-induced liver injuries due to dietary supplements is currently about 20%. Furthermore, bodybuilding and weight-loss supplements account for almost half of these injuries (62). Among emergency department visits for adverse events related to dietary supplements in the United States, approximately 25% were due to weight-loss products (63). Two classes of adverse effects may occur. Supplements can have components according to the product description that cause certain side effects. Supplements may also be intentionally spiked with unlisted or illegal compounds or drugs such as anabolic steroids. These are so-called adulterated supplements. Supplements containing declared compounds that have not been tested adequately for safety can also be declared adulterated by the FDA. Some researchers argued that adulterated supplements should not be considered real dietary supplements (64). Yet such supplements exist and can readily be obtained, such as over the Internet. Furthermore, they may be more likely to give real physiological effects desired by the consumer owing to the pharmacological efficiency of anabolic steroids or other drugs incorporated in the supplements. Medical providers and toxicologists should therefore be aware of symptoms elicited by these compounds.

Supplements with some documented weight-loss effects are those containing extracts of plants in the genus *Ephedra*, also known as ma huang. Extracts contain the sympathomimetic alkaloids ephedrine, pseudoephedrine, methylephedrine, and norephedrine. Some of these alkaloids are currently incorporated in common pharmaceutical medications. For example, pseudoephedrine is included as a nasal decongestant in several brands of cold and allergy medication in the United States, such as Claritin-D and Sudafed. A comprehensive meta-analysis of clinical trials showed that ephedra or ephedrine-containing products overall led to modest short-term weight loss of approximately 0.9 kg/month more than that observed with placebo (65). There were significant 2.2–3.6-fold increased risks of adverse effects in the form of psychiatric symptoms, autonomic hyperactivity, heart palpitations, and upper gastrointestinal symptoms (65). Autonomic hyperactivity, including symptoms such as tremors, jitteriness, insomnia, and increased perspiration, was very common, affecting more than 20% of subjects taking ephedrine. However, caffeine may

have contributed to some of the side effects, as caffeine was included in most of the ephedrine-containing products. A review of 140 adverse event reports submitted to the FDA between June 1, 1997, and March 31, 1999, resulted in 31% of cases considered to be definitely or probably related to the intake of dietary supplements with ephedra alkaloids (66). The most common event was hypertension, but they also included cases of arrhythmia, myocardial infarction, stroke, and cardiac arrest, with 3 deaths and 7 permanent disabilities. It led the authors to conclude, "dietary supplements that contain ephedra alkaloids pose a serious health risks to some users" (66, p. 1838). More than a dozen cases of liver injury have also been reported after intake of ephedra preparations (67). Dietary supplements with ephedra were banned by the FDA in 2004 (68).

One of the compounds that has until recently been widely incorporated in sports supplements is 1,3-dimethylamylamine (DMAA). It was used in roughly 200 supplements, with more than $100 million in sales in 2010 (69). DMAA is a pharmaceutical developed and patented by Eli Lilly and Company as a nasal inhaler for rhinitis with "the desirable properties of both ephedrine and amphetamine" (70, p. 1). It has sympathomimetic and vasoconstrictive properties. Producers of dietary supplements have listed the compound as a natural component of Geranium plants (e.g., as geranium extract) (71). However, the presence of DMAA in plants has not been verified, leading to the conclusion that DMAA in supplements is generated by chemical synthesis (72). DMAA has further been banned as a performance-enhancing drug by the World Anti-Doping Agency (73). One version of the weight-loss supplement OxyELITE Pro from USPlabs, LLC contained DMAA in addition to ingredients such as caffeine, *Bauhinia purpurea*, *Bacopa monnieri*, *Cirsium oligophyllum*, and rauwolscine (yohimbe) extract. Studies that were supported financially by USPlabs, LLC with a small number of healthy volunteers suggested that this supplement formulation could increase lipolysis, metabolic rate, heart rate, and systolic blood pressure in the short term (2 h) as well as lead to small decreases in appetite, body weight, and body mass index after intake for 8 weeks (74). Accidental intake of supplements with DMAA, mainly in children, have caused relatively mild adverse effects such as tachycardia, nausea, and vomiting (75). However, serious cardiovascular events after DMAA intake have also been reported. Recreational use of DMAA in New Zealand has been associated with cases of cerebral hemorrhage (76, 77). Furthermore, three cases of cardiac arrest occurred during physical exercise in the military and in a gym following intake of DMAA-containing supplements (71, 78). Two of the events eventually led to the deaths of US soldiers. Although it cannot be proven that DMAA was the causative agent for all the adverse events, DMAA clearly does indeed have cardiovascular effects such as vasoconstriction and elevation of blood pressure (79, 80). Following receipt of 42 adverse event reports on products with DMAA, the FDA in April 2012 sent warning letters to 10 manufacturers of DMAA-containing supplements stating that because the safety of DMAA had not been documented, the products were adulterated, according to US law (81).

In 2013, a series of severe hepatic liver disease cases occurred in individuals from Hawaii taking the weight-loss supplement OxyELITE Pro from USPlabs, LLC (82, 83). Eight previously healthy individuals presented with symptoms such as fatigue, nausea, abdominal pain, and jaundice. Levels of alanine transaminase and total bilirubin were elevated. Of three patients developing fulminant hepatic failure, two required a liver transplant and one died. A subsequent outbreak investigation conducted by the Hawaii State Department of Health in collaboration with the US Centers for Disease Control and Prevention (CDC) and FDA identified a total of 36 cases of acute hepatitis in individuals exposed to OxyELITE Pro (84). All had dark urine and most had jaundice, loss of appetite, and fatigue. In 2013, additional cases of acute liver injury in patients who had taken OxyELITE Pro were observed in the United States in the Drug-Induced Liver Injury Network (DILIN) prospective study and among military personnel in Southern California (85, 86). From January 2011 to February 2014, the FDA received adverse event reports for

114 consumers who had used OxyELITE Pro. Fifty-five cases (48%) were classified as having liver disease likely due to OxyELITE Pro (87). The incidence of liver disease seemed to spike after February 2013. Tallying cases of acute hepatitis of unknown etiology occurring from April 1, 2013, to December 5, 2013, in individuals who consumed OxyELITE Pro in the 60 days prior to illness resulted in 69 case patients, of whom 32 were hospitalized, 3 received liver transplants, and 1 died (88). The spike in liver disease coincided with a reformulation of OxyELITE Pro to DMAA-free versions of OxyELITE Pro (New Formula and Super Thermo) that, instead of DMAA, contained the compound aegeline (83). Aegeline is an alkaloidal-amide occurring naturally in the bael tree (*Aegle marmelos*) with antihyperglycemic effects in a diabetic rat model (89). However, there do not appear to be relevant studies on the effects of aegeline in humans. In a warning letter to USPlabs, LLC, the FDA wrote that aegeline should be classified as a new dietary ingredient because it was not marketed in the United States before October 15, 1994. As the company further had failed "to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury," the FDA deemed the aegeline-containing supplements to be adulterated (90). The aegeline-containing supplements were subsequently recalled (91).

It is unclear if the aegeline in OxyELITE Pro was the hepatotoxic agent causing the outbreak of liver disease. Although feeding rats *A. marmelos* plant material has resulted in liver lesions in the form of centrilobular congestion and hydropic degeneration (92), it is unknown whether this was due to aegeline or other compounds. The aegeline in OxyELITE Pro may further have been a synthetic compound of unknown purity (93). As no other known hepatotoxic agents were found in OxyELITE Pro, the specific causative agent remains unidentified (88). The link between the observed cases of hepatitis and OxyELITE intake has also been questioned. Teschke & Eickhoff (94) argue that clinicians describing the first cases were not sufficiently fastidious in excluding other causes of liver disease such as acetaminophen toxicity, liver cirrhosis, and viral hepatitis, and that causality scores on the Roussel Uclaf Causality Assessment Method were inflated to show that OxyELITE Pro was the probable cause for the cases.

It is remarkable that OxyELITE Pro products have been adulterated with two different compounds, DMAA and aegeline. There is even a recent notification from the FDA that a batch of OxyELITE Pro Super Thermogenic was found to contain fluoxetine, also known as Prozac (95). Although USPlabs, LLC has claimed that this latter batch represented a counterfeit product not manufactured by the company, it certainly underscores that segments of the dietary supplement business employ shady or even criminal manufacturing and business practices that result in consumers being exposed to untested or undeclared compounds.

OxyELITE Pro is not the only multi-ingredient dietary supplement associated with liver injury. The LiverTox database lists incidences of hepatotoxicity attributed to the brands Slimquick, Herbalife, Hydroxycut, and Move Free (67). Earlier versions of Hydroxycut contained ephedra, but otherwise the exact mechanisms of injury are generally unknown, even though some of the cases may be due to the content of green tea, *Aloe vera*, and Chinese skullcap.

The examples listed above represent adverse effects caused by ingredients listed by the producers. More insidious is the addition of unlisted ingredients or drugs to dietary supplements. Antiobesity drugs rimonabant, orlistat, and sibutramine or analogs thereof have been found in weight-loss supplements from Germany, Turkey, China, and Poland (96). Side effects of these drugs, such as panic attacks, psychotic episodes, and increases in blood pressure and heart rate, in the case of sibutramine, may therefore also be encountered in individuals using such adulterated supplements.

Body-building supplements are quite often adulterated with anabolic steroids that are modified variants of androgens designed to increase muscle mass. Studies from 2001 and 2002 based on nutritional supplements purchased in 13 countries, including the United States, indicated that about 15% of nutritional supplements contained undeclared anabolic androgenic steroids (97).

Adverse effects of anabolic steroids include cardiomyopathy, altered serum lipids, acne, swollen breast tissues in men, and hepatotoxicity (98). Several patients have developed hepatic cholestasis after intake of anabolic androgens (99, 100). In the United States, the DILIN was established in 2003 to identify and characterize cases of hepatotoxicity caused by dietary supplements and drugs, with the exception of acetaminophen. Among 847 cases whose liver injuries were confirmed to be caused by drugs or supplements, 45 (5.3%) were due to the use of bodybuilding supplements (101). This latter group consisted exclusively of males who all had jaundice, and most (84%) had pruritus. The pattern of liver injury resembled that of bland cholestasis. Compared to other cases, the levels of serum alanine transaminase, aspartate aminotransferase, and alkaline phosphatase were lower, but the levels of total bilirubin were higher, and the patients were jaundiced for longer periods of time (101). The mechanism whereby anabolic steroids induce hepatotoxicity is poorly understood, but researchers have hypothesized it is mediated by activation of the androgen receptor in hepatic cells, leading to upregulation of the rate-limiting enzyme carnitine palmitoyltransferase 1 in mitochondrial fatty acid β-oxidation, increased oxidative stress, and ultimately mitochondrial degeneration and hepatotoxicity (98).

BOTANICAL SUPPLEMENTS

Traditional herbal medicine can be said to be the precursor both for drugs used in modern medicine that are based on plant compounds (such as aspirin and morphine) and for contemporary botanical dietary supplements. Herbal and botanical products have sustained popularity given the fact that these natural (i.e., derived from plant root, leaves, or bark) substances were among the oldest therapeutics. Estimates published by the CDC as part of the National Health and Nutrition Examination Survey 2003–2006 reported that 20% of adults use a supplement containing at least one botanical ingredient (102). A common motivation for taking these substances is to "improve overall health" (3, p. 357). Accordingly, the FDA regulates the majority of botanicals as dietary supplements and not as drugs developed for the treatment or prevention of specific maladies (103). Botanical use is correlated with nonsmoking and higher self-reported health (3). Alarmingly, patients frequently do not report herbal supplement use to primary care physicians (104), a concern because many botanical supplements may interact with prescribed medications. On their own, bioactive constituents of botanicals can have acute adverse effects that require hospitalization. This review describes acute adverse effects and herb-drug interactions of the most common botanical and herbal supplements.

Because of their plant-based derivation, botanical supplements consist of a mixture of organic compounds. Only a fraction of these compounds are biologically active, with a small subset of the active compounds having therapeutic and/or toxic mechanisms of action. **Table 1** presents a list of commonly used and researched botanical supplements, their primary active constituents, typical use and dosage, and reported adverse effects.

Concurrent exposure to other compounds (e.g., pharmaceuticals, smoking) and the heterogeneity of herbal supplements often obfuscates the determination of toxic mechanisms in clinical cases, even when doses of the supplement are reported. As such, reports of adverse effects directly attributable to botanicals are generally rare (105). In most such cases, effects are mild (e.g., nausea, fatigue, and headache). However, more serious clinical cases have appeared, most often relating to adverse effects falling under the general category of drug-induced liver injury and its associated mechanisms, namely mitochondrial dysfunction, oxidative stress, and alteration of bile acid homeostasis.

Black cohosh (*Cimicifuga racemosa*) has been associated with jaundice and liver failure in menopausal women (106). Immunohistochemistry of biopsy samples revealed pathological

Table 1 Usage and dose information for selected botanicals

Botanical	Scientific name	Popular use	Active components	Typical dose (mg/day)[a]
Echinacea	Genus *Echinacea* (nine known species)	Immunostimulant	Chicoric acid, alkylamides	900–1,000 (124)
Garlic	*Allium sativum*	Antioxidant; antihypertension	Allicin, adenosine	4,000 fresh; 600–900 powder (124)
Ginkgo biloba	*Ginkgo biloba*	Memory improvement; lowering blood pressure	Terpenoids (ginkgolides)	120–600 (125)
Ginseng	*Panax ginseng*	Overall health; antistress	Ginsenosides	150–200 (124)
Green tea extract	*Camellia sinensis*	Antiproliferative; antioxidant	Catechins (ECGC, ECG)	1,300 (catechols) (126)
Saw palmetto	*Serenoa repens*	Treatment of benign prostatic hypertrophy	Various phytosterols	100–900 (127)
St. John's wort	*Hypericum perforatum*	Antidepressant	Hyperforin, hypericin	900–1,800 (128)
Milk thistle	*Silybum marianum*	DILI; high cholesterol	Silymarin	160–800 (129)
Kava kava	*Piper methysticum*	Reducing anxiety	Kavalactones	45–1,200 (108)
Black cohosh	*Cimicifuga racemosa*, *Actaea racemosa*	Alleviating postmenopausal symptoms	Triterpene glycosides	6.5–160 (130)
Valerian	*Valeriana officinalis*	Reducing anxiety	Valepotriates (terpene alcohols)	1,500 (131)
Yohimbe	*Pausinystalia yohimbe*	Stimulant; erectile dysfunction treatment	Yohimbine	30–50 (132)
Goldenseal	*Hydrastis canadensis*	Treatment of cold/respiratory infection; alleviate menstrual complications	Hydrastine, berberine	750–6,000 (124)

Abbreviations: DILI, drug-induced liver injury; ECG, epicatechin gallate; ECGC, epigallocatechin gallate.
[a]Example doses listed are from clinical studies or medical information websites (where noted), as recommended for indicated use. Doses may vary depending on usage.

oxidative stress. These results are consistent with in vivo data showing increases in mitochondrial reactive oxygen species and decreased catalase activity with *C. racemosa* treatment in a rat menopausal model (107). Similarly, numerous case reports of kava kava detail liver toxicity sometimes requiring transplants (reviewed in 108). Candidate mechanisms for kava kava liver toxicity include depletion of glutathione (increasing oxidative stress) and inhibition of cyclooxygenases (mitochondrial dysfunction) (109). Saw palmetto use has been associated with cholestatic hepatitis; subsequent alterations in bile secretion have been linked to pancreatitis (110). Cholestatic symptoms were also seen in patients with acute liver failure who had ingested echinacea, although a specific mechanism has not been hypothesized (111). Valerian use induced jaundice that was reversed by steroid administration in a 57-year-old man (112). Case reports have presented a variety of other nonhepatic symptoms following botanical use. A bodybuilder taking yohimbe prior to a workout session suffered a seizure with tachycardia and hypertension, consistent with yohimbine's sympathomimetic properties (113). A 68-year-old woman taking milk thistle presented with symptoms of exacerbated hemochromatosis (iron overload) that dissipated when she stopped taking the supplement. However, this patient was genetically predisposed to hemochromatosis, and physicians withdrew excess iron via phlebotomy concomitant with her cessation of milk thistle use (114). Ginseng use was implicated in a transient ischemia attack in a 64-year-old man,

Table 2 Notable pharmacokinetic herb-drug interactions

Enzyme	Botanical	Dose per day; duration	Probe; effect
CYP3A4	Goldenseal	600 mg; 12 days	CsA; inhibition (133)
	Echinacea	1,600 mg; 8 days	MDZ; induction of hepatic 3A4, inhibition of intestinal 3A4 (134)
	St. John's wort	Various	Various; induction (135)
	Ginseng	1,000 mg; 28 days	MDZ; induction (136)
	Green tea extract	800 mg; 4 weeks	Buspirone; inhibition (137)
CYP2D6	Goldenseal	2,700 mg; 28 days	Debrisoquine; inhibition (138)
		3,210 mg; 14 days	Debrisoquine; inhibition (139)
CYP1A2	Echinacea	1,600 mg; 8 days	Caffeine; inhibition (134)
		1,600 mg; 28 days	Caffeine; inhibition ($P = 0.07$, not clinically relevant) (140)
	Kava kava	1,000–4,000 mg; >6 years (analysis following 30-day cessation)	Caffeine; inhibition (141)
CYP2E1	Garlic	1,500 mg; 28 days	CZX; inhibition (142)
	Kava kava	2,000 mg; 28 days	CZX; inhibition (138)
CYP2C19	Ginkgo biloba	280 mg; 12 days	OPZ; induction (genotype effect[a]) (143)
	St. John's wort	900 mg; 14 days	*S*-mephenytoin; induction (genotype effect[a]) (144)
CYP2C9	Milk thistle	420 mg; 14 days	Losartan; inhibition (genotype effect[a]) (145)
	Goldenseal	900 mg; 14 days	Losartan; inhibition (146)
	Echinacea	1,600 mg; 8 days	Tolbutamide; inhibition (134)
OATP1A2	Green tea extract	637 mg; 14 days	Nadolol; inhibition (147)
P-glycoprotein	Garlic	1,200 mg; 21 days	Saquinavir; induction (148)
	Ginkgo biloba	360 mg; 14 days	Talinolol; inhibition (149)
	St. John's wort	2,000–4,000 mg; 14 days	Digoxin; induction (150)

Abbreviations: CsA: cyclosporin A; CYP, cytochrome P450; CZX: chlorzoxazone; MDZ: midazolam; OATP1A2, organic anion-transporting polypeptide 1A2; OPZ: omeprazole.

[a]Genotype effect: effect seen in high-efficiency but not low-efficiency metabolizers.

although there was no evaluation of the mechanism (115). In other cardiovascular outcomes, black cohosh was deemed probably responsible for observed bradycardia in a 59-year-old woman. Slow heart rate is a reported side effect of black cohosh (116). The wide variety of compounds identified in black cohosh make it difficult to elucidate mechanisms, although the authors of the above case study speculated that black cohosh regulates heart rate via activation of serotonin receptors, consistent with experimental results (117). Both garlic and ginkgo biloba use have been involved in several cases of excessive bleeding. For example, a 71-year-old man had persistent surgical bleeding that was attributed to indulgent garlic ingestion prior to the operation (118). Furthermore, aged garlic extract inhibits platelet aggregation (119). Ginkgolide B, an active component of gingko biloba, has been shown to inhibit platelet aggregating factor, and men and women taking ginkgo biloba have suffered spontaneous bleeding (120).

Compared to the above outcomes, more is known about potential herb-drug interactions. Pharmacologically active compounds in botanicals are, like drugs, substrates of metabolizing enzymes. As such, induction or suppression of relevant metabolizing enzymes can affect the pharmacokinetics of drugs and may warrant contraindications by health-care providers. In vitro studies have

implicated activation of the pregnane X receptor and the aryl hydrocarbon receptor as a common mechanism among several botanicals in inducing cytochrome P450 (CYP) expression (121–123). Clinical trials aim to identify such herb-drug pharmacokinetic interactions and their enzymatic targets via coadministration of an enzyme-specific probe. Investigated targets include the CYP enzymes, organic anion transporter proteins, and the P-glycoprotein ATP binding cassette transporter. **Table 2** presents a representative list of several well-characterized herb-drug interactions from clinical studies of human volunteers.

CONCLUSIONS

The market for dietary supplements and nutraceuticals taken to improve the health or well-being of the customer is enormous. However, these products are not necessarily safe for everybody. Like regular drugs, supplements with active ingredients that provide a physiological or pharmacological effect are likely to also cause adverse effects in susceptible individuals. More attention to adverse effects and potential interactions is needed to avoid serious medical outcomes. Users and physicians alike should consult updated literature before beginning or advising a regimen involving these substances. Medical providers should be aware that a large fraction of the general population takes dietary supplements. They should therefore request information from patients about their supplement intake to provide optimal medical care.

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LITERATURE CITED

1. Mueller C. 1999. The regulatory status of medical foods and dietary supplements in the United States. *Nutrition* 15:249–51
2. ODS (Off. Diet. Suppl.). 2011. *Dietary Supplements: Background Information*. Bethesda, MD: Natl. Inst. Health, Off. Diet. Suppl. **https://ods.od.nih.gov/factsheets/DietarySupplements-HealthProfessional/**
3. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. 2013. Why US adults use dietary supplements. *JAMA Intern. Med.* 173:355–61
4. Moyer MW. 2014. Vitamins of trial. *Nature* 510:462–64
5. Funk C. 1912. The etiology of the deficiency diseases. Beri-beri, polyneuritis in birds, epidemic dropsy, scurvy, experimental scurvy in animals, infantile scurvy, ship beri-beri, pellagra. *J. State Med.* 20:341–68
6. Woo JJY. 2007. Adverse event monitoring and multivitamin-multimineral dietary supplements. *Am. J. Clin. Nutr.* 85:323S–24S
7. Velicer CM, Ulrich CM. 2008. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. *J. Clin. Oncol.* 26:665–73
8. Knapik JJ, Steelman RA, Hoedebecke SS, Farina EK, Austin KG, Lieberman HR. 2014. A systematic review and meta-analysis on the prevalence of dietary supplement use by military personnel. *BMC Complement. Altern. Med.* 14:143

9. Mulholland CA, Benford DJ. 2007. What is known about the safety of multivitamin-multimineral supplements for the generally healthy population? Theoretical basis for harm. *Am. J. Clin. Nutr.* 85:318S–22S
10. Guallar E, Stranges S, Mulrow C, Appel LJ, Miller ER III. 2013. Enough is enough: Stop wasting money on vitamin and mineral supplements. *Ann. Intern. Med.* 159:850–51
11. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. 2013. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: an updated systematic evidence review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 159:824–34
12. Ziegler EE, Filer LJ Jr., eds. 1996. *Present Knowledge in Nutrition*. Washington, DC: Int. Life Sci. Inst. Nutr. Found. 7th ed.
13. de Kruijk JR, Notermans NC. 2005. *Gevoelsstoornissen veroorzaakt door multivitaminepreparaten* [Sensory disturbances caused by multivitamin preparations]. *Ned. Tijdschr. Geneeskd.* 149:2541–44
14. Bairati I, Meyer F, Gélinas M, Fortin A, Nabid A, et al. 2005. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. *J. Clin. Oncol.* 23:5805–13
15. Miller ER III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. 2005. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann. Int. Med.* 142:37–46
16. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, et al. 1996. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N. Engl. J. Med.* 334:1150–55
17. Alpha-Tocopherol Beta Carotene Cancer Prev. Study Group. 1994. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N. Engl. J. Med.* 330:1029–35
18. Rapola JM, Virtamo J, Ripatti S, Haukka JK, Huttunen JK, et al. 1998. Effects of α tocopherol and β carotene supplements on symptoms, progression, and prognosis of angina pectoris. *Heart* 79:454–58
19. Rapola JM, Virtamo J, Haukka JK, Heinonen OP, Albanes D, et al. 1996. Effect of vitamin E and beta carotene on the incidence of angina pectoris: a randomized, double-blind, controlled trial. *JAMA* 275:693–98
20. Melhus H, Michaëlsson K, Kindmark A, Bergström R, Holmberg L, et al. 1998. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann. Intern. Med.* 129:770–78
21. Rothman KJ, Moore LL, Singer MR, Nguyen U-SDT, Mannino S, Milunsky A. 1995. Teratogenicity of high vitamin A intake. *N. Engl. J. Med.* 333:1369–73
22. Ramanathan VS, Hensley G, French S, Eysselein V, Chung D, et al. 2010. Hypervitaminosis A inducing intra-hepatic cholestasis—a rare case report. *Exp. Mol. Pathol.* 88:324–25
23. Barton JC, Lee PL, West C, Bottomley SS. 2006. Iron overload and prolonged ingestion of iron supplements: clinical features and mutation analysis of hemochromatosis-associated genes in four cases. *Am. J. Hematol.* 81:760–67
24. Swanson CA. 2003. Iron intake and regulation: implications for iron deficiency and iron overload. *Alcohol* 30:99–102
25. Spector AA, Kim H-Y. 2015. Discovery of essential fatty acids. *J. Lipid Res.* 56:11–21
26. Bang HO, Dyerberg J, Nielsen AB. 1971. Plasma lipid and lipoprotein pattern in Greenlandic west-coast Eskimos. *Lancet* 297:1143–45
27. Sierra S, Lara-Villoslada F, Olivares M, Jiménez J, Boza J, Xaus J. 2004. *La expresión de IL-10 interviene en la regulación de la respuesta inflamatoria por los ácidos grasos omega 3* [Il-10 expression is involved in the regulation of the immune response by omega 3 fatty acids]. *Nutr. Hosp.* 19:376–82
28. Leaf A, Kang JX, Xiao Y-F. 2008. Fish oil fatty acids as cardiovascular drugs. *Curr. Vasc. Pharmacol.* 6:1–12
29. Gogos CA, Skoutelis A, Kalfarentzos F. 2000. The effects of lipids on the immune response of patients with cancer. *J. Nutr. Health Aging* 4:172–75
30. Harris WS, Isley WL. 2001. Clinical trial evidence for the cardioprotective effects of omega-3 fatty acids. *Curr. Atheroscler. Rep.* 174–79
31. Glück T, Alter P. 2016. Marine omega-3 highly unsaturated fatty acids: from mechanisms to clinical implications in heart failure and arrhythmias. *Vascul. Pharmacol.* 82:11–19
32. Gross BW, Gillio M, Rinehart CD, Lynch CA, Rogers FB. 2017. Omega-3 fatty acid supplementation and warfarin: a lethal combination in traumatic brain injury. *J. Trauma Nurs.* 24:15–18

33. Buckley MS, Goff AD, Knapp WE. 2004. Fish oil interaction with warfarin. *Ann. Pharmacother.* 38:50–53
34. Fang N, Yu S, Badger TM. 2004. Comprehensive phytochemical profile of soy protein isolate. *J. Agric. Food Chem.* 52:4012–20
35. Messina M. 2016. Soy and health update: evaluation of the clinical and epidemiologic literature. *Nutrients* 8:754
36. Badger TM, Gilchrist JM, Pivik RT, Andres A, Shankar K, et al. 2009. The health implications of soy infant formula. *Am. J. Clin. Nutr.* 89:1668S–72S
37. Chen A, Rogan WJ. 2004. Isoflavones in soy infant formula: a review of evidence for endocrine and other activity in infants. *Annu. Rev. Nutr.* 24:33–54
38. Harlid S, Adgent M, Jefferson WN, Panduri V, Umbach DM, et al. 2017. Soy formula and epigenetic modifications: analysis of vaginal epithelial cells from infant girls in the IFED study. *Environ. Health Perspect.* 125:447–52
39. Adgent MA, Daniels JL, Rogan WJ, Adair L, Edwards LJ, et al. 2012. Early-life soy exposure and age at menarche. *Paediatr. Perinat. Epidemiol.* 26:163–75
40. Adgent MA, Daniels JL, Edwards LJ, Siega-Riz AM, Rogan WJ. 2011. Early-life soy exposure and gender-role play behavior in children. *Environ. Health Perspect.* 119:1811–16
41. Andres A, Moore MB, Linam LE, Casey PH, Cleves MA, Badger TM. 2015. Compared with feeding infants breast milk or cow-milk formula, soy formula feeding does not affect subsequent reproductive organ size at 5 years of age. *J. Nutr.* 145:871–75
42. Gilchrist JM, Moore MB, Andres A, Estroff JA, Badger TM. 2010. Ultrasonographic patterns of reproductive organs in infants fed soy formula: comparisons to infants fed breast milk and milk formula. *J. Pediatr.* 156:215–20
43. Strom BL, Schinnar R, Ziegler EE, Barnhart KT, Sammel MD, et al. 2001. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 286: 807–14
44. Hamilton-Reeves JM, Vazquez G, Duval SJ, Phipps WR, Kurzer MS, Messina MJ. 2010. Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: results of a meta-analysis. *Fertil. Steril.* 94:997–1007
45. Akingbemi BT, Braden TD, Kemppainen BW, Hancock KD, Sherrill JD, et al. 2007. Exposure to phytoestrogens in the perinatal period affects androgen secretion by testicular Leydig cells in the adult rat. *Endocrinology* 148:4475–88
46. Tan KAL, Walker M, Morris K, Greig I, Mason JI, Sharpe RM. 2006. Infant feeding with soy formula milk: effects on puberty progression, reproductive function and testicular cell numbers in marmoset monkeys in adulthood. *Hum. Reprod.* 21:896–904
47. Sharpe RM, Martin B, Morris K, Greig I, McKinnell C, et al. 2002. Infant feeding with soy formula milk: effects on the testis and on blood testosterone levels in marmoset monkeys during the period of neonatal testicular activity. *Hum. Reprod.* 17:1692–703
48. Allred CD, Allred KF, Ju YH, Virant SM, Helferich WG. 2001. Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. *Cancer Res.* 61:5045–50
49. McCarver G, Bhatia J, Chambers C, Clarke R, Etzel R, et al. 2011. NTP-CERHR expert panel report on the developmental toxicity of soy infant formula. *Birth Defects Res. B Dev. Reprod. Toxicol.* 92:421–68
50. Perry DL, Spedick JM, McCoy TP, Adams MR, Franke AA, Cline JM. 2007. Dietary soy protein containing isoflavonoids does not adversely affect the reproductive tract of male cynomolgus macaques (*Macaca fascicularis*). *J. Nutr.* 137:1390–94
51. Ronis MJ, Gomez-Acevedo H, Blackburn ML, Cleves MA, Singhal R, Badger TM. 2016. Uterine responses to feeding soy protein isolate and treatment with 17β-estradiol differ in ovariectomized female rats. *Toxicol. Appl. Pharmacol.* 297:68–80
52. Miousse IR, Sharma N, Blackburn M, Vantrease J, Gomez-Acevedo H, et al. 2013. Feeding soy protein isolate and treatment with estradiol have different effects on mammary gland morphology and gene expression in weanling male and female rats. *Physiol. Genom.* 45:1072–83

53. Zhang J, Lazarenko OP, Wu X, Tong Y, Blackburn ML, et al. 2012. Differential effects of short term feeding of a soy protein isolate diet and estrogen treatment on bone in the pre-pubertal rat. *PLOS ONE* 7:e35736
54. Ronis MJJ, Chen Y, Shankar K, Gomez-Acevedo H, Cleves MA, et al. 2011. Formula feeding alters hepatic gene expression signature, iron and cholesterol homeostasis in the neonatal pig. *Physiol. Genom.* 43:1281–93
55. Singhal R, Shankar K, Badger TM, Ronis MJ. 2009. Hepatic gene expression following consumption of soy protein isolate in female Sprague-Dawley rats differs from that produced by 17β-estradiol treatment. *J. Endocrinol.* 202:141–52
56. Ronis M, Hennings L, Gomez-Acevedo H, Badger T. 2014. Different responses to soy and estradiol in the reproductive system of prepubertal male rats and neonatal male pigs. *FASEB J.* 28:373.5
57. Weaver CM, Alekel DL, Ward WE, Ronis MJ. 2012. Flavonoid intake and bone health. *J. Nutr. Gerontol. Geriatr.* 31:239–53
58. Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, et al. 2009. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur. J. Clin. Pharmacol.* 65:331–41
59. Mahady G, Parrot J, Lee C, Yun G, Dan A. 2003. Botanical dietary supplement use in peri- and post-menopausal women. *Menopause* 10:65–72
60. Lieberman HR, Stavinoha TB, McGraw SM, White A, Hadden LS, Marriott BP. 2010. Use of dietary supplements among active-duty US Army soldiers. *Am. J. Clin. Nutr.* 92:985–95
61. Hoyte CO, Albert D, Heard KJ. 2013. The use of energy drinks, dietary supplements, and prescription medications by United States college students to enhance athletic performance. *J. Community Health* 38:575–80
62. Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. 2017. Liver injury from herbal and dietary supplements. *Hepatology* 65:363–73
63. Geller AI, Shehab N, Weidle NJ, Lovegrove MC, Wolpert BJ, et al. 2015. Emergency department visits for adverse events related to dietary supplements. *New Engl. J. Med.* 373:1531–40
64. Brown AC. 2017. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. *Food Chem. Toxicol.* 107:449–71
65. Shekelle PG, Hardy ML, Morton SC, Maglione M, Mojica WA, et al. 2003. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA* 289:1537–45
66. Haller CA, Benowitz NL. 2000. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N. Engl. J. Med.* 343:1833–38
67. US Natl. Libr. Med. 2016. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda, MD: Natl. Inst. Health, US Natl. Libr. Med. **https://livertox.nlm.nih.gov/index.html**
68. FDA (US Food Drug Adm.). 2004. *FDA issues regulation prohibiting sale of dietary supplements containing ephedrine alkaloids and reiterates its advice that consumers stop using these products*. News Release, Febr. 6. **https://wayback.archive-it.org/7993/20170113025516/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108242.htm**
69. Cohen PA. 2012. DMAA as a dietary supplement ingredient. *Arch. Intern. Med.* 172:1038–39
70. Shonle HA, Ewald R. 1944. *Aminoalkanes*. US Patent No. 2350318
71. Eliason MJ, Eichner A, Cancio A, Bestervelt L, Adams BD, Deuster PA. 2012. Case reports: death of active duty soldiers following ingestion of dietary supplements containing 1,3-dimethylamylamine (DMAA). *Mil. Med.* 177:1455–59
72. Di Lorenzo C, Moro E, Dos Santos A, Uberti F, Restani P. 2013. Could 1,3 dimethylamylamine (DMAA) in food supplements have a natural origin? *Drug Test. Anal.* 5:116–21
73. World Anti-Doping Agency. 2016. *The World Anti-Doping Code: International Standard. Prohibited List January 2017*. Montreal: World Anti-Doping Agency. **https://www.wada-ama.org/sites/default/files/resources/files/2016-09-29_-_wada_prohibited_list_2017_eng_final.pdf**
74. McCarthy CG, Canale RE, Alleman RJ Jr., Reed JP, Bloomer RJ. 2012. Biochemical and anthropometric effects of a weight loss dietary supplement in healthy men and women. *Nutr. Metab. Insights* 5:13–22
75. Forrester MB. 2013. Exposures to 1,3-dimethylamylamine-containing products reported to Texas poison centers. *Hum. Exp. Toxicol.* 32:18–23

76. Gee P, Tallon C, Long N, Moore G, Boet R, Jackson S. 2012. Use of recreational drug 1,3 dimethylamylamine (DMAA) associated with cerebral hemorrhage. *Ann. Emerg. Med.* 60:431–34
77. Gee P, Jackson S, Easton J. 2010. Another bitter pill: a case of toxicity from DMAA party pills. *N. Z. Med. J.* 123:124–27
78. Karnatovskaia LV, Leoni JC, Freeman ML. 2015. Cardiac arrest in a 21-year-old man after ingestion of 1,3-DMAA-containing workout supplement. *Clin. J. Sport Med.* 25:e23–25
79. Swanson EE, Chen KK. 1946. Comparison of pressor action of aliphatic amines. *J. Pharmacol. Exp. Ther.* 88:10–13
80. Bloomer RJ, Harvey IC, Farney TM, Bell ZW, Canale RE. 2011. Effects of 1,3-dimethylamylamine and caffeine alone or in combination on heart rate and blood pressure in healthy men and women. *Phys. Sportsmed.* 39:111–20
81. FDA (US Food Drug Adm.). 2012. *FDA challenges marketing of DMAA products for lack of safety evidence*. News Release, Apr. 27. **https://wayback.archive-it.org/7993/20170112012624/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302133.htm**
82. Park SY, Viray M, Johnston D, Taylor E, Chang A, et al. 2013. Notes from the field: acute hepatitis and liver failure following the use of a dietary supplement intended for weight loss or muscle building-May-October 2013. *MMWR Morb. Mortal Wkly. Rep.* 62:817–19
83. Roytman MM, Pörzgen P, Lee CL, Huddleston L, Kuo TT, et al. 2014. Outbreak of severe hepatitis linked to weight-loss supplement OxyELITE Pro. *Am. J. Gastroenterol.* 109:1296–98
84. Johnston DI, Chang A, Viray M, Chatham-Stephens K, He H, et al. 2014. Hepatotoxicity associated with the dietary supplement OxyELITE Pro™—Hawaii, 2013. *Drug Test. Anal.* 8:319–27
85. Heidemann LA, Navarro VJ, Ahmad J, Hayashi PH, Stolz A, et al. 2016. Severe acute hepatocellular injury attributed to OxyELITE Pro: a case series. *Dig. Dis. Sci.* 61:2741–48
86. Foley S, Butlin E, Shields W, Lacey B. 2014. Experience with OxyELITE pro and acute liver injury in active duty service members. *Dig. Dis. Sci.* 59:3117–21
87. Klontz KC, DeBeck HJ, LeBlanc P, Mogen KM, Wolpert BJ, et al. 2015. The role of adverse event reporting in the FDA response to a multistate outbreak of liver disease associated with a dietary supplement. *Public Health Rep.* 130:526–32
88. Chatham-Stephens K, Taylor E, Chang A, Peterson A, Daniel J, et al. 2017. Hepatotoxicity associated with weight loss or sports dietary supplements, including OxyELITE Pro™—United States, 2013. *Drug Test. Anal.* 9:68–74
89. Narender T, Shweta S, Tiwari P, Papi Reddy K, Khaliq T, et al. 2007. Antihyperglycemic and antidyslipidemic agent from *Aegle marmelos*. *Bioorg. Med. Chem. Lett.* 17:1808–11
90. FDA (US Food Drug Adm.). 2013. *Warning Letter*. Silver Spring, MD: US Food and Drug Administration. **https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm371203.htm**
91. FDA (US Food Drug Adm.). 2013. *OxyElite Pro supplements recalled*. News Release, Nov. 18. **http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm374742.htm**
92. Arseculeratne SN, Gunatilaka AAL, Panabokke RG. 1985. Studies on medicinal plants of Sri Lanka. Part 14: toxicity of some traditional medicinal herbs. *J. Ethnopharmacol.* 13:323–35
93. US Natl. Libr. Med. 2016. Drug record: OxyELITE Pro. In *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda, MD: Natl. Inst. Health, US Natl. Libr. Med. **https://livertox.nlm.nih.gov/OxyELITEPro.htm**
94. Teschke R, Eickhoff A. 2016. The Honolulu liver disease cluster at the Medical Center: its mysteries and challenges. *Int. J. Mol. Sci.* 17:476
95. Tritten TJ. 2015. Pulled twice from exchanges, OxyElite Pro supplement now found to contain Prozac drug. *Stars and Stripes*, Mar. 2. **https://www.stripes.com/news/pulled-twice-from-exchanges-oxyelite-pro-supplement-now-found-to-contain-prozac-drug-1.332350**
96. Skalicka-Woźniak K, Georgiev MI, Orhan IE. 2016. Adulteration of herbal sexual enhancers and slimmers: the wish for better sexual well-being and perfect body can be risky. *Food Chem. Toxicol.* In press. **https://doi.org/10.1016/j.fct.2016.06.018**
97. Geyer H, Parr MK, Koehler K, Mareck U, Schänzer W, Thevis M. 2008. Nutritional supplements cross-contaminated and faked with doping substances. *J. Mass Spectrom.* 43:892–902

98. Bond P, Llewellyn W, Van Mol P. 2016. Anabolic androgenic steroid-induced hepatotoxicity. *Med. Hypotheses* 93:150–53
99. Krishnan PV, Feng Z-Z, Gordon SC. 2009. Prolonged intrahepatic cholestasis and renal failure secondary to anabolic androgenic steroid-enriched dietary supplements. *J. Clin. Gastroenterol.* 43:672–75
100. Shah NL, Zacharias I, Khettry U, Afdhal N, Gordon FD. 2008. Methasteron-associated cholestatic liver injury: clinicopathologic findings in 5 cases. *Clin. Gastroenterol. Hepatol.* 6:255–58
101. Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, et al. 2014. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology* 60:1399–408
102. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, et al. 2011. Dietary supplement use in the United States, 2003–2006. *J. Nutr.* 141:261–66
103. FDA (US Food Drug Adm.). 2016. *Botanical Drug Development: Guidance for Industry*. Silver Spring, MD: US Food Drug Adm. **http://www.fda.gov/downloads/Drugs/Guidances/UCM458484.pdf**
104. Wu C-H, Wang C-C, Kennedy J. 2011. Changes in herb and dietary supplement use in the U.S. adult population: a comparison of the 2002 and 2007 National Health Interview Surveys. *Clin. Ther.* 33:1749–58
105. Di Lorenzo C, Ceschi A, Kupferschmidt H, Lude S, De Souza Nascimento E, et al. 2015. Adverse effects of plant food supplements and botanical preparations: a systematic review with critical evaluation of causality. *Br. J. Clin. Pharmacol.* 79:578–92
106. Enbom ET, Le MD, Oesterich L, Rutgers J, French SW. 2014. Mechanism of hepatotoxicity due to black cohosh (*Cimicifuga racemosa*): histological, immunohistochemical and electron microscopy analysis of two liver biopsies with clinical correlation. *Exp. Mol. Pathol.* 96:279–83
107. Campos LB, Gilglioni EH, Garcia RF, Brito MdN, Natali MRM, et al. 2012. *Cimicifuga racemosa* impairs fatty acid β-oxidation and induces oxidative stress in livers of ovariectomized rats with renovascular hypertension. *Free Radic. Biol. Med.* 53:680–89
108. Teschke R. 2010. Kava hepatotoxicity—a clinical review. *Ann. Hepatol.* 9:251–65
109. Clouatre DL. 2004. Kava kava: examining new reports of toxicity. *Toxicol. Lett.* 150:85–96
110. Hamid S, Rojter S, Vierling J. 1997. Protracted cholestatic hepatitis after the use of prostata. *Ann. Intern. Med.* 127:169–70
111. Gabranis I, Koufakis T, Papakrivos I, Batala S. 2015. Echinacea-associated acute cholestatic hepatitis. *J. Postgrad. Med.* 61:211–12
112. Kia YH, Alexander S, Dowling D, Standish R. 2016. A case of steroid-responsive valerian-associated hepatitis. *Intern. Med. J.* 46:118–19
113. Giampreti A, Lonati D, Locatelli C, Rocchi L, Campailla MT. 2009. Acute neurotoxicity after yohimbine ingestion by a body builder. *Clin. Toxicol.* 47:827–29
114. Whittington C. 2007. Exacerbation of hemochromatosis by ingestion of milk thistle. *Can. Fam. Physician.* 53:1671–73
115. Martínez-Mir I, Rubio E, Morales-Olivas FJ, Palop-Larrea V. 2004. Transient ischemic attack secondary to hypertensive crisis related to *Panax ginseng*. *Ann. Pharmacother.* 38:1970
116. McKenzie SC, Rahman A. 2010. Bradycardia in a patient taking black cohosh. *Med. J. Aust.* 193:479–81
117. Burdette JE, Liu J, Chen S-N, Fabricant DS, Piersen CE, et al. 2003. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J. Agric. Food Chem.* 51:5661–70
118. Woodbury A, Sniecinski R. 2016. Garlic-induced surgical bleeding: How much is too much? *A&A Case Rep.* 7:266–69
119. Rahman K, Lowe GM, Smith S. 2016. Aged garlic extract inhibits human platelet aggregation by altering intracellular signaling and platelet shape change. *J. Nutr.* 146:410S–15S
120. Bent S, Goldberg H, Padula A, Avins AL. 2005. Spontaneous bleeding associated with *Ginkgo biloba*: a case report and systematic review of the literature. *J. Gen. Intern. Med.* 20:657–61
121. Tirona RG, Bailey DG. 2006. Herbal product–drug interactions mediated by induction. *Br. J. Clin. Pharmacol.* 61:677–81
122. Pang X, Cheng J, Krausz KW, Guo D-A, Gonzalez FJ. 2011. Pregnane X receptor-mediated induction of Cyp3a by black cohosh. *Xenobiotica* 41:112–23
123. Chang TKH. 2009. Activation of pregnane X receptor (PXR) and constitutive androstane receptor (CAR) by herbal medicines. *AAPS J.* 11:590–601

124. Hermann R, von Richter O. 2012. Clinical evidence of herbal drugs as perpetrators of pharmacokinetic drug interactions. *Planta Med*. 78:1458–77
125. Mayo Clinic. 2013. Dosing. In *Drugs and Supplements: Ginkgo (Ginkgo biloba)*. Rochester, MN: Mayo Found. Med. Educ. Res. (MFMER). **http://www.mayoclinic.org/drugs-supplements/ginkgo/dosing/hrb-20059541**
126. Chen IJ, Liu C-Y, Chiu J-P, Hsu C-H. 2016. Therapeutic effect of high-dose green tea extract on weight reduction: a randomized, double-blind, placebo-controlled clinical trial. *Clin. Nutr.* 35:592–99
127. Mayo Clinic. 2013. Dosing. In *Drugs and Supplements: Saw palmetto (Serenoa repens, Serenoa serrulata)*. Rochester, MN: Mayo Found. Med. Educ. Res. (MFMER). **http://www.mayoclinic.org/drugs-supplements/saw-palmetto/dosing/hrb-20059958**
128. Mayo Clinic. 2013. Dosing. In *Drugs and Supplements: St. John's wort (Hypericum perforatum)*. Rochester, MN: Mayo Found. Med. Educ. Res. (MFMER). **http://www.mayoclinic.org/drugs-supplements/st-johns-wort/dosing/hrb-20060053**
129. Mayo Clinic. 2013. Dosing. In *Drugs and Supplements: Milk Thistle (Silybum marianum)*. Rochester, MN: Mayo Found. Med. Educ. Res. (MFMER). **http://www.mayoclinic.org/drugs-supplements/milk-thistle/dosing/hrb-20059806**
130. Mayo Clinic. 2013. Dosing. In *Drugs and Supplements: Black cohosh (Cimicifuga racemosa, Actaea racemosa)*. Rochester, MN: Mayo Found. Med. Educ. Res. (MFMER). **http://www.mayoclinic.org/drugs-supplements/black-cohosh/dosing/hrb-20058861**
131. Gharib M, Samani LN, Panah ZE, Naseri M, Bahrani N, Kiani K. 2015. The effect of valeric on anxiety severity in women undergoing hysterosalpingography. *Glob. J. Health Sci.* 7:358–63
132. Drugs.com. 2009. *Yohimbe*. Dallas, TX: Drugs.com. **https://www.drugs.com/npp/yohimbe.html**
133. Wu X, Li Q, Xin H, Yu A, Zhong M. 2005. Effects of berberine on the blood concentration of cyclosporin A in renal transplanted recipients: clinical and pharmacokinetic study. *Eur. J. Clin. Pharmacol.* 61:567–72
134. Gorski JC, Huang SM, Pinto A, Hamman MA, Hilligoss JK, et al. 2004. The effect of echinacea (*Echinacea purpurea* root) on cytochrome P450 activity in vivo. *Clin. Pharmacol. Ther.* 75:89–100
135. Whitten DL, Myers SP, Hawrelak JA, Wohlmuth H. 2006. The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. *Br. J. Clin. Pharmacol.* 62:512–26
136. Malati CY, Robertson SM, Hunt JD, Chairez C, Alfaro RM, et al. 2012. Influence of *Panax ginseng* on cytochrome P450 (CYP)3A and P-glycoprotein (P-gp) activity in healthy participants. *J. Clin. Pharmacol.* 52:932–39
137. Chow HHS, Hakim IA, Vining DR, Crowell JA, Cordova CA, et al. 2006. Effects of repeated green tea catechin administration on human cytochrome P450 activity. *Cancer Epidemiol. Biomark. Prev.* 15:2473–76
138. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, et al. 2005. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clin. Pharmacol. Ther.* 77:415–26
139. Gurley BJ, Swain A, Hubbard MA, Hartsfield F, Thaden J, et al. 2008. Supplementation with goldenseal (*Hydrastis canadensis*), but not kava kava (*Piper methysticum*), inhibits human CYP3A activity in vivo. *Clin. Pharmacol. Ther.* 83:61–69
140. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, et al. 2004. In vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: *Citrus aurantium*, *Echinacea purpurea*, milk thistle, and saw palmetto. *Clin. Pharmacol. Ther.* 76:428–40
141. Russmann S, Lauterburg BH, Barguil Y, Choblet E, Cabalion P, et al. 2005. Traditional aqueous kava extracts inhibit cytochrome P450 1A2 in humans: protective effect against environmental carcinogens? *Clin. Pharmacol. Ther.* 77:453–54
142. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, et al. 2002. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. *Clin. Pharmacol. Ther.* 72:276–87
143. Yin OQP, Tomlinson B, Waye MMY, Chow AHL, Chow MSS. 2004. Pharmacogenetics and herb-drug interactions: experience with Ginkgo biloba and omeprazole. *Pharmacogenetics* 14:841–50
144. Wang L-S, Zhu B, El-Aty AMA, Zhou G, Li Z, et al. 2004. The influence of St John's Wort on CYP2C19 activity with respect to genotype. *J. Clin. Pharmacol.* 44:577–81

145. Han Y, Guo D, Chen Y, Chen Y, Tan ZR, Zhou HH. 2009. Effect of silymarin on the pharmacokinetics of losartan and its active metabolite E-3174 in healthy Chinese volunteers. *Eur. J. Clin. Pharmacol.* 65:585–91
146. Guo Y, Chen Y, Tan ZR, Klaassen CD, Zhou HH. 2012. Repeated administration of berberine inhibits cytochromes P450 in humans. *Eur. J. Clin. Pharmacol.* 68:213–17
147. Misaka S, Yatabe J, Müller F, Takano K, Kawabe K, et al. 2014. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. *Clin. Pharmacol. Ther.* 95:432–38
148. Hajda J, Rentsch KM, Gubler C, Steinert H, Stieger B, Fattinger K. 2010. Garlic extract induces intestinal P-glycoprotein, but exhibits no effect on intestinal and hepatic CYP3A4 in humans. *Eur. J. Pharm. Sci.* 41:729–35
149. Fan L, Tao G-Y, Wang G, Chen Y, Zhang W, et al. 2009. Effects of Ginkgo biloba extract ingestion on the pharmacokinetics of talinolol in healthy Chinese volunteers. *Ann. Pharmacother.* 43:944–49
150. Mueller SC, Uehleke B, Woehling H, Petzsch M, Majcher-Peszynska J, et al. 2004. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. *Clin. Pharmacol. Ther.* 75:546–57