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# ADVERSE EFFECTS OF NUTRACEUTICALS AND DIETARY SUPPLEMENTS

**Martin J. J. Ronis**, **Kim B. Pedersen**, and **James Watt**

Department of Pharmacology & Experimental Therapeutics, Louisiana State University Health Sciences Center – New Orleans, Louisiana 70112

## Abstract

Some form of dietary supplement is taken by over 70% of Americans 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 FDA prior to production or sales. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), FDA is restricted to adverse report monitoring post-marketing. 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, it is rare that patients 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 potential for drug interactions.

### Keywords

Toxicity; multivitamin/multimineral; soy protein isolate; isoflavones; bodybuilding supplements; herb-drug interaction

## INTRODUCTION

Dietary supplements are products that are ingested in addition to the regular diet in order to provide additional health-promoting nutrients. In the US, 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

Corresponding author contact information: Martin Ronis, Department of Pharmacology & Experimental Therapeutics, Louisiana State University Health Sciences Center – New Orleans, Louisiana 70112, mronis@lsuhsc.edu, Phone: (504) 568-4740. kpeder@lsuhsc.edu, and jwatt4@lsuhsc.edu, respectively.

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M.R., K.P. and J.W. prepared the text and tables. M.R. supervised and finalized the manuscript.

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The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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supplements. The term “nutraceutical” is not defined by U.S. law, but is generally understood to be a purified product derived from a human food source, which is purported to provide extra health benefits beyond the basic nutritional value found in foods.

The Food and Drug Administration (FDA) regulates dietary supplements in a markedly different way than 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 for a drug. No clinical trials are required. Ingredients sold in the US 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 US 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, maintain health, and, especially among women, for bone health. The most commonly used supplements were multivitamin/mineral supplements, calcium supplements, and omega-3/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 doesn’t 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. The current review is not intended to be comprehensive report of all known adverse effect for all dietary supplements. Instead, we have selected to discuss adverse events for the most commonly used supplements such as vitamins, minerals, omega-3/fish oil, soy protein, and plant-derived antioxidant and anti-inflammatory nutraceuticals. We also discuss weight-loss and body building supplements, and various botanical supplements which have been associated with more severe adverse effects.

Since 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

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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 20th century, it had become clear that nutrition consisting solely of carbohydrates, fats, and proteins is insufficient for maintaining health. The term “vitamine” was coined by Casimir Funk 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/multimineral, vitamin and mineral supplements are the most widely utilized 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). Since dietary micronutrient deficiency is increasingly rare in developed counties, most supplement consumers actually have excess vitamin and mineral intake. Despite widespread belief that vitamin and mineral supplements are health beneficial, 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, cognitive decline and effects on overall mortality (10,11). Indeed, on the contrary, there is evidence for possible harm based on 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/d 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 8 related tocopherols and tocotrienols of which α-tocopherol is the form generally used in supplements. Doses of 800–1200 mg/d can result in bleeding associated with antiplatelet action and doses above 1200 mg/d 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 ATBC study (17), male smokers receiving β-carotene supplements had significantly increased risk of lung cancer. The ABTC study further showed that prostate cancer incidence and mortality were increased in male alcohol users consuming the supplement. An

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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 intra-hepatic cholestasis in a patient with chronic hypervitaminosis A after 12 years of supplement consumption which resolved after supplements were ceased (22). In addition to toxicity from excess vitamin consumption, toxicity can arise from excess consumption of minerals. In particular, there is an increasing 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 that is rich in polyunsaturated omega-3 fatty acids had significantly lower levels of plasma total lipids, plasma cholesterol, plasma triglycerides and pre-β-lipoprotein (= 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 (DHA and EPA) purified from fish oils have become widely utilized 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 anti-cancer and cardioprotective effects (29,30). However, the therapeutic benefits on cardiovascular diseases are still controversial due 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 1–2,000 mg/d and there is little evidence of toxicity. However, simultaneous consumption of fish liver oils which 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, 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 U.S. 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

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ongoing debate with regard to the potential safety of SPI. This is related primarily to the presence of weakly estrogenic compounds – the isoflavones genistein and daidzein which are among the 100 phytochemicals which 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 post-menopausal 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). Several clinical studies of SPI and soy formula toxicity have been conducted. Epigenome-wide DNA methylation analysis of vaginal cells from cow- 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 vs. 12.8 years) but less female-typical play in soy formula-fed girls (39,40). In contrast, data from a longitudinal ultrasound study of breast, cow's 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 et al. (46,47) reported that marmoset monkeys fed soy infant formula had suppressed serum testosterone concentrations. Increased testis size, and Leydig cell numbers/testis were also observed in these monkeys at adulthood consistent with compensated Leydig cell failure. In adult female ovariectomized mice, feeding SPI was shown to increase 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 (CERHR) established by the National Toxicology Program (NTP) and the National Institute for Environmental Health Sciences (NIEHS). 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 soy protein isolate (SPI), the sole protein source in soy formulas revealed no effects on sex organ weights, no effects on serum sex steroids concentrations and no effects on fertility (36). Moreover, chronic feeding studies with SPI in adult male cynomolgus macaque monkeys also are reported to have had 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, in prepubertal male and female rats and in neonatal piglets in which we have utilized genomics analysis either with Affymetrix chips or using RNAseq 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–

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10%) representing specific subsets of E2 regulated pathways, indicative of actions similar to those of selective estrogen receptor modulators (SERMS), 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 anti-oxidant or anti-inflammatory properties which 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, and catechins from tea and quercetin. There is little data to suggest that these compounds are toxic. However, metabolites of EGCG – 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 have 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 post-menopausal women, menopausal women have increasingly turned to use of 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). Since 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 population becomes overweight and obese, there is a huge market for weight-loss products, including dietary supplements. Among military service members, athletes and bodybuilders it is also common to ingest dietary sports supplements intended to burn fat and increase performance, muscle mass or strength. As examples, 53% of active-duty US Army soldiers report using at least one dietary supplement per week (60), and 64% of college students participating in athletics use 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. In a recent review, it is estimated that the proportion of drug-induced liver injuries that are due to dietary

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supplements is currently around 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 US, around 25% were due to weight loss products (63). There are two classes of adverse effects that 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 adequately tested for safety can also be declared adulterated by the US Food and Drug Administration (FDA). It has been argued that adulterated supplements shouldn't be considered real dietary supplements (64). Yet, such supplements exist and can readily be obtained e.g. over the internet. Furthermore, they may be more likely to give real physiological effects desired by the consumer due to the pharmacological efficiency of anabolic steroids or other drugs incorporated in the supplements. Medical providers and toxicologists should be therefore be aware of symptoms elicited by these compounds.

Body weight supplements with some documented weight-loss effects were those containing extracts of the plant *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 US like 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 better than 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 events reports submitted to the FDA between June 1, 1997 and March 31, 1999 resulted in 31% of cases considered to the 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 that, "dietary supplements that contain ephedra alkaloids pose a serious health risks to some users". 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 & Co. as a nasal inhaler for rhinitis with "the desirable properties of both ephedrine and amphetamine" (70). It has sympathomimetic and vasoconstrictive properties. Producers of dietary supplements have listed the compound as a natural

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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 the compound 1,3-dimethylamylamine (DMAA) in addition to ingredients such as caffeine, *Bauhinia purpurea*, *Bacopa monniera*, *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 BMI 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, there are three cases of cardiac arrest occurring 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. While it cannot be proven that DMAA is the causative agent for all the adverse events, it is clear that DMAA does indeed have cardiovascular effects such as vasoconstriction and elevation of blood pressure (79,80). Following receipt of 42 adverse events reports on products with DMAA, the FDA in April 2012 sent warning letters to 10 manufacturers of DMAA-containing supplements stating that since 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 was observed in individuals from Hawaii awaiitaking 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 Department of Health in collaboration with the 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. Around 2013, additional cases of acute liver injury in patients that had taken OxyELITE Pro were observed in the US 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 that had used OxyELITE Pro. 55 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 one 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

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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, the FDA wrote that aegeline should be classified as a “new dietary ingredient” since it was not marketed in the US 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. While feeding rats *Aegle 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 was 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 and Eickhoff 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 (RUCAM) were inflated to show that OxyELITE Pro was the probable cause for the cases (94).

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). While 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. Anti-obesity drugs rimonabant, orlistat, and sibutramine or analogues thereof have been found in weight-loss supplements from Germany, Turkey, China, and Poland (96). Side effects of these drugs, like 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

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2002 based on nutritional supplements purchased in 13 countries, including the US, indicated that around 15% of nutritional supplements contained non-declared 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 US, the Drug-Induced Liver Injury Network (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 use of bodybuilding supplements (101). This latter group was characterized by consisting exclusively of males that all had jaundice and where most (84%) had pruritus. The pattern of liver injury resembled that of bland cholestasis. Compared to other cases, the levels of serum ALT, AST and ALP were lower, but the levels of total bilirubin were higher, and they were jaundiced for longer periods of time (101). The mechanism whereby the anabolic steroids induce hepatotoxicity is poorly understood, but it has been hypothesized to be mediated by activation of the androgen receptor in hepatic cells, leading to upregulation of the rate-limiting enzyme, CPT1, 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 for both 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). Accordingly, the US Food and Drug Administration 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 non-smoking 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 is 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

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in clinical cases, even where 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 (DILI) 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 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 that 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 non-hepatic 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, though there was no evaluation as to 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). Gingkolide 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 (PXR) and the aryl hydrocarbon receptor (AhR) as a common mechanisms among several botanicals in

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inducing cytochrome P450 (CYP) expression (121–123). Clinical trials aim to identify such herb-drug pharmacokinetic interactions and their enzymatic targets via co-administration of an enzyme-specific probe. Investigated targets include the CYP enzymes, organic anion transporter (OAT) proteins, and the P-glycoprotein (P-gp) 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, they 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 in order 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 general population take dietary supplements. They should therefore request information from patients about their supplement intake in order to provide optimal medical care.

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**TABLE 1.**

Usage and dose information for selected botanicals

| Botanical | Scientific name | Popular use | Active components | Typical dose ($day^{-1}$)[a] |
|---|---|---|---|---|
| Echinacea | Genus *Echinacea* (9 known species) | Immunostimulant | Chicoric acid, alkylamids | 900–1000 mg (124) |
| Garlic | *Allium sativum* | Antioxidant; anti-hypertension | Allicin, adenocine | 4000 mg fresh; 600–900 mg powder (124) |
| Ginkgo biloba | *Ginkgo biloba* | Memory improvement; lowering blood pressure | Terpenoids (ginkolides) | 120–600 mg (125) |
| Ginseng | *Panax ginseng* | Overall health; anti-stress | Ginsenosides | 150–200 mg (124) |
| Green tea extract | *Camellia sinensis* | Anti-proliferative; antioxidant | Catechins (ECGC, ECC) | 1300 mg (catechols) (126) |
| Saw Palmetto | *Serenoa repens* | Treatment of benign prostatic hypertrophy | Various phytosterols | 100–900 mg (127) |
| St. John's Wort | *Hypericum perforatum* | Anti-depressant | Hyperforin, hypericin | 900–1800 mg (128) |
| Milk Thistle | *Silybum marianum* | DILI; high cholesterol | Silymarin | 160–800 mg (129) |
| Kava kava | *Piper methysticum* | Reducing anxiety | Kavalactones | 45–1200 mg (108) |
| Black cohosh | *Cimicifuga racemosa, Actaea racemosa* | Alleviating postmenopausal symptoms | Triterpene glycosides | 6.5–160 mg (130) |
| Valerian | *Valeriana officinalis* | Reducing anxiety | Valepotriates (terpine alcohols) | 1500 mg (131) |
| Yohimbe | *Pausinystalia johimbe* | Stimulant; erectile dysfunction treatment | Yohimbine | 30–50 mg (132) |
| Goldenseal | *Hydrastis canadensis* | Treatment of cold/respiratory infection; alleviate menstrual complications | Hydrastine, berberine | 750–6000 mg (124) |

[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.

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**TABLE 2.**

Notable pharmacokinetic herb-drug interactions

| Enzyme | Botanical | Dose (day$^{-1}$), duration | Probe;[a] effect[b] |
|---|---|---|---|
| CYP3A4 | Goldenseal | 600 mg, 12 d | CsA; inhibition (133) |
| | Echinacea | 1600 mg, 8 d | MDZ; induction of hepatic 3A4, inhibition of intestinal 3A4 (134) |
| | St. John's Wort | Various | Various; induction (135) |
| | Ginseng | 2000 mg, 28 d | MDZ; induction (136) |
| | Green Tea extract | 800 mg, 4 wk | Buspirone; inhibition (137) |
| CYP2D6 | Goldenseal | 2700 mg, 28 d | Debrisoquine; inhibition (138) |
| | | 3210 mg, 14 d | Debrisoquine; inhibition (139) |
| CYP1A2 | Echinacea | 1600 mg, 8 d | Caffeine; inhibition (134) |
| | | 1600 mg, 28 d | Caffeine; inhibition (p = 0.07, not clinically relevant) (140) |
| | Kava kava | 1000–4000 mg, >6 years (analysis following 30-day cessation) | Caffeine; inhibition (141) |
| CYP2E1 | Garlic | 1500 g, 28 d | CZX; inhibition (142) |
| | Kava kava | 2000 mg, 28 d | CZX; inhibition (138) |
| CYP2C19 | Ginkgo biloba | 280 mg, 12 d | OPZ; induction (genotype effect) (143) |
| | St. John's Wort | 900 mg, 14 d | S-mephenytoin; induction (genotype effect) (144) |
| CYP2C9 | Milk thistle | 420 mg, 14 d | Losartan; inhibition (genotype effect) (145) |
| | Goldenseal | 900 mg, 14 d | Losartan; inhibition (146) |
| | Echinacea | 1600 mg, 8 d | Tolbutamide; inhibition (134) |
| OATP1A2 | Green Tea extract | 637 mg, 14 d | Nadolol; inhibition (147) |
| P-glycoprotein | Garlic | 1200 mg, 21 d | Saquinavir; induction (148) |
| | Ginkgo biloba | 360 mg, 14 d | Talinolol; inhibition (149) |
| | St. John's Wort | 2000–4000 mg, 14 d | Digoxin; induction (150) |

[a]MDZ: midazolam; CZX: chlorzoxazone; OPZ: omeprazole; CsA: cyclosporin A.

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