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Dietary or Nutritional Supplements Associated Adverse Effects and Toxicity

Review Article

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Abstract

In recent decades, physical inactivity, work pressure and stress as well as change in food habits have led to the deterioration of public health. Therefore, dietary supplements, especially the herbal products have gained much popularity due to their nutritional as well as therapeutic benefits. However, the efficacy and safety of such marketed products can be affected by factors like, the presence of multiple ingredients, impurities, adulterations, processing methods or storage conditions. In general, the herbal formulations are not regulated as strictly as the conventional therapeutics or prescription drugs. Therefore, herbal nutraceuticals or supplements associated morbidity remains a serious health issue with broad implications for nutritionists, dieticians, clinicians, pharma industries and food or drug regulatory authorities. This article presents an overview of the adverse clinical effects and toxicological outcomes of some of the commonly used herbal supplements, such as Aloe, green tea, Ginseng, Ginkgo, Tongkat Ali, Flaxseed, St. John's wort and Withania.

Keywords: Dietary Supplements, Herbal Nutraceuticals, Adverse Effects, Toxicity, Drug regulation

Introduction

Dietary or nutritional supplements are health-protective natural products that are consumed in addition to the conventional foods to compensate dietary deficiencies [1]. These include plant or animal products, multivitamins, minerals, essential amino acids, unsaturated fatty acids, hormones, enzymes, and metabolites commercialized as pills, tablet, capsules or syrups [2,3]. Globally, physical inactivity, work pressure and stress as well as change in food habits, especially the increased consumption of nutrient-deficient and high-energy junk foods have led to the deterioration of public health. In recent decades therefore, dietary supplement products have gained much popularity due to their nutritional as well as therapeutic benefits. According to a 2013 survey, the Asia-Pacific region including the Middle-East was the largest market of such products accounting for about 31.2% of the global market, followed by Europe (30%) and North America (25.4%) [4]. Notably, of the several such products, Ginseng sales in the U.S. have been reported to be over $300 million, annually [5]. The U.S. Food and Drug Administration (FDA) has estimated the availability of over 29,000 different dietary supplements to about 68% consumers, as well as annual introduction of approximately 1,000 new products [6]. Notably, the efficacy and safety of dietary supplements can be affected by several factors such as the presence of multiple ingredients, impurities, adulterations, methods of processing or storage conditions. In recent times therefore, adverse clinical effects associated to such products have been well documented in the literature [2,3,7]. This article presents an overview of the adverse clinical effects and toxicological outcomes of some of the commonly used herbal supplements.

Commonly used herbal supplements and their adverse clinical effects

Though, herbals are generally believed to be more effective and safer than prescription drugs, over 55 species of 46 plant families, including their toxic phytochemicals have been identified to cause hepatic, gastrointestinal, cardiovascular, and neuronal toxicity [8,9]. While conventional drugs or therapeutic agents are approved by drug regulatory authorities only after pre-clinical validations and human trials, majority of herbal products are sold without any scientific evidence of their efficacy and safety. According to the American Association of Poison Control Center (AAPCC) 2006 report, there were 76,364 cases of adverse effects including few deaths due to dietary supplements [10]. Therefore, herbal supplements associated morbidity remains a serious public health issue with broad implications for nutritionists, dieticians, clinicians, pharma industries and food or drug regulatory authorities.

Aloe:

The Aloe plant (*Aloe vera*) is widely used as a dietary supplement in a variety of foods and medications, being one of the largest herbal industries worldwide [11,12]. In food industry, Aloe is used in the manufacture of functional foods; especially health drinks [13] whereas it is sold as pharmaceutical products as tablets, capsules, gels and ointments [14]. Phytochemical analysis of Aloe pulp (gel or latex) has revealed presence of various pharmacologically active polysaccharides and phenolic compounds, notably anthraquinones attribute to their high antioxidative and hypoglycemic efficacies [4,15,16].

Though several case reports on toxicity or hypersensitivity of Aloe are known, there are no published controlled studies on its toxicity is available [17]. Aloe gel can cause skin irritation, hives, cramping and diarrhea to those who are allergic to onion and tulip plants [12]. The first case of Aloe consumption associated hepatitis had been reported in Germany [18]. This was followed by reports from Turkey [19], the U.S. [20], Argentina [21] and South Korea [22].

Green Tea:

Green tea (*Camellia sinensis*) is a global beverage which is often sold as herbal supplement, especially for its high antioxidant and nerve stimulating benefits attributed to its catechins, caffeine, minerals, vitamins, amino acids, and carbohydrates [23,24,25,26]. Moreover, green tea and its constituents were also found to be effective in preventing oxidative stress and neurological problems. Studies using animal models have shown activities of green tea catechins against degenerative diseases, hyperlipidemia and carcinomas [27,28].

Though green tea and its constituents are beneficial up to a certain dose, consumption of higher doses may cause some adverse effects, including experimental liver toxicity [29]. Animal study has shown that higher intake of green tea might cause oxidative damage of pancreas and liver in hamsters, attributed to catechins [30,31]. In addition, high intake of green tea extract has been reported to induced thyroid enlargement and modified the plasma concentrations of the thyroid hormones in rats [32,33].

Ginseng:

Ginseng (*Panax ginseng* and *Panax quinquefolius*) root is marketed as dietary supplement known for immune-modulating functions, attributed to its high content saponins, ginsenosides, phenolic and compounds, including carbohydrates and carotenoids [34,35]. In addition, Ginseng consumption has been also reported for anti-aging, anti-diabetic and anti-cancer activities as well as in curing cardiovascular diseases and sexual dysfunction [36].

High doses and long-term usage of Ginseng has been reported with few adverse effects such as morning diarrhea, skin eruption, sleeplessness, edema, decreased appetite, depression, altered blood pressure, headache, mastalgia, nausea, and vaginal bleeding [7]. However, the toxicological assessments of Ginseng have suggested a relatively low frequency of organ toxicity [38]. Notably, interaction of Ginseng with aspirin, trazodone and warfarin has been observed with hyphema, high blood pressure, unconsciousness, coma, and intracerebral hemorrhage [39].

Ginkgo:

Ginkgo (*Ginkgo biloba*) leaf extract is marketed as a health protective nutritional or dietary supplement, and is one of the most commonly used herbals worldwide [40]. While it is sold as over-the-counter preparation in Germany [41], it is regulated as foodstuff or food supplement in the U.S. [42]. Its standardized special formulation (EGb761) containing various flavone glycosides and terpenoids, is often prescribed in Europe as a nootropic agent in old age and dementia [43]. In addition, Ginkgo is also perceived to improve memory, microcirculation, hypoxia tolerance, and blood viscosity [41].

In general, Ginkgo consumption is safe and well-tolerated at the recommended maximal dose [44]. However, in some cases mild adverse effects like, headache, heart palpitations, constipation etc. have been reported. Notably, raw Ginkgo seeds contain potentially toxic cyanogenic glycosides that can cause a serious allergic skin reaction such as acute generalized exanthematous pustulosis and convulsions [45,46]. In addition, bleeding, seizure and serotonin syndrome could be potential consequences of ginkgo toxicity (https://www.ncbi.nlm.nih.gov/books/NBK541024/). Gingko have been also associated with an increased risk of bleeding in patients who are on warfarin or aspirin treatment [39].

Tongkat Ali:

Eurycoma longifolia Jack, commercially known as Tongkat Ali is a very popular herbal or dietary supplement [47, 48]. It is generally sold as raw crude powder of dried roots without involving any other chemical processing procedures [49]. A wide range of bioactive compounds such as eurycomanone, eurycomanol, eurycomalactone, canthine-6-one alkaloid, tannins, quanissoids, and triterpenes have been isolated from its roots [50,51]. These compounds are attributed to its antipyretic, antimalarial, antibacterial, and antitumor properties and aphrodisiac effect in males [52-54]. In addition, Tongkat has been also documented for its antioxidative properties due to high concentrations of superoxide dismutase [55, 56]. Notably, it has gained considerable attention in Malaysia where it is used as health additive in coffee and other drinks [57].

In clinical studies, a daily dose of about 100 mg/day is considered quite safe without any adverse effects [56]. In subacute toxicity study, Tongkat at doses above 1200 mg/kg (equivalent to 8200 mg taken by a 70 kg man) caused pathological changes in rat liver [54].

Flaxseed:

Flax (*Linum usitatissimum*) is categorized as a functional food. Milled flaxseed supplementation of the diet has several healthy benefits, of which cardiovascular disease and cancer are the best-researched areas ([8]. Flaxseed is a rich source of the omega-3 fatty acid, alpha linolenic acid and secoisolariciresinol diglucoside, which are attributed to dyslipidemia, anti-inflammatory, anti-oxidative, and anti-diabetes salutations [59]. Also, flaxseed tablets or drinks are shown to be effective in weight-loss through hunger suppression [60].

Although no toxicity of flaxseed has ever been reported in clinical studies, its ingredients like cyanogenic glycosides and linatine are potentially toxic [61]. Nonetheless, these compounds are instable when subjected to thermal and mechanical processes, including boiling and microwave cooking [62,63].

St. John's Wort:

St. John's Wort (*Hypericum perforatum*) is an effective dietary supplement for treating anxiety, depression, mood disorders, insomnia, attention-deficit hyperactivity disorder, somatic

symptom disorder, stress and inflammation [64,65,66,67]. In addition to hypericin and hyperforin, which are the major bioactive compounds, several flavonoids, phloroglucinols, napthodianthrones, xanthones and proanthocyanidins have been also identified as active principles in the plant [64,66]. Notably therefore, St. John's wort has gained competing status as the only herbal antidepressant alternative to standard antidepressant drugs [68]. In recent times, it has become one of the high selling herbal supplements in North America, Europe and Asia [68].

Interaction of St. John's Wort with other conventional drugs such as warfarin, phenoprocumon, cyclosporine, oral contraceptives, theophylline, digoxin, indinavir and lamivudine have been reported to cause headache, nausea, vomiting, epigastric pain, anxiety, irregular menstrual bleeding, and intrinsic hepatotoxicity etc. [9].

Withania:

Withania (*Withania somnifera*), also known as Indian Ginseng (Ashwagandha) or Winter Cherry is a dietary supplement. Its root decoction is especially used as health restorative nutrient by pregnant and nursing women for its milk thickening property [69]. In addition; it has anti-stress, neuroprotective, immunomodulatory, analgesic, anti-inflammatory, and cardioprotective effects [70]. The pharmacological salutations of Withania roots are attributed to withanine, withasomnin, withanolide and sitoindosides [71].

In general, Withania is considered safe and without any major adverse effects. However, several cases of liver injury have been reported in patients who consumed marketed herbal formulations containing Withania (https://www.ncbi.nlm.nih.gov/books/NBK548536/).

Regulations for herbal dietary supplements:

In the U.S., dietary supplements are defined and regulated according to the 1994 Dietary Supplement Health and Education Act (DSHEA) 1994 [72,73]. Herbal supplements are regulated by the both DSHEA and FDA, but not as strictly as prescription or over-the-counter drugs. Also, the efficacy of a marketed dietary supplement is not required under the U.S. law [74]. Nonetheless, DSHEA has recommended the legal definition, labeling requirements, and process for adverse effects reporting for such dietary supplements. FDA has also issued formal guidance to ensure that their methods for preparation, composition, purity, packaging, labeling, and storage are well documented. The manufactures must therefore, (i) accurately label all ingredients and ensure of any contaminants, (ii) provide research to support the claimed benefit, and include a disclaimer that the FDA hasn't evaluated the claim, (iii) avoid making false or unsupported claims to sell such products. In addition, The Dietary Supplement and Nonprescription Drug Consumer Protection Act (NDCPA) 2006 has further, enforced the manufacturers to report any adverse side effects of their products to the FDA to further determine their safety. With these controls, the regulatory authorities provide assurance to the consumers that the marketed herbal supplements meet certain quality standards, and can remove toxic or health compromising products from the market. Notably, while such guidelines are strictly followed in the U.S., these are either unregulated or partially regulated in other countries. In view of the growing evidences of herbal or dietary supplements associated adverse clinical effects, other countries, especially those with high consumers must implement the FDA, DSHEA or NDCPA guidelines.

Conclusion:

Generally, consumption of herbal or dietary supplement products are believed to be more effective and safer than conventional therapeutics. In recent decades however, adverse clinical effects associated to such products have been well documented. Therefore, herbal nutraceuticals or supplements associated morbidity remains a serious issue with broad implications for nutritionists, dieticians, clinicians, pharma industries and health authorities. In view of this, a comprehensive experimental or pre-clinical studies on cytotoxicity, genotoxicity, dose tolerance, safety pharmacology and toxicokinetic must be carried out prior to commercialization of such products. Though the U.S. drug authorities have implemented certain regulatory controls, these cannot guarantee the safety of certain herbal supplements. Most importantly, consumers should be educated and made aware that the marketed herbal supplements may contain ingredients with significant adverse effects.

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