



Effectively Managing the Co-ingestion of Dietary Supplements and Prescription Drugs

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Abstract

According to recent surveys, over half of American adults take at least one dietary supplement (DS), with usage increasing with age. Healthcare providers should be aware of which DS products their patients are taking in order to best manage their overall care. While DS can be used to complement and enhance the actions of traditional medicine, they may be contraindicated when taken concomitant with prescribed medications. Herein, example DS-drug interactions associated with common conditions are discussed, as well as two hypothetical applications of DS.

Keywords: dietary Supplement; Co-ingestion; FDA

Introduction

A dietary supplement (DS), as defined within the Dietary Supplement Health and Education Act (DSHEA) of 1994, is a product containing vitamins, minerals, and other natural products (e.g., herbs, amino acids, and metabolites) that are taken orally to fill nutritional gaps [1]. Dietary supplement regulation is a complex, global issue [2]. In the United States, the Food and Drug Administration (FDA) classifies DS as a special subcategory of food, not as drugs. As such, although DS are regulated by the FDA, they do not have the same stringency and oversight as prescription medication [3]. The FDA also does not approve DS prior to being sold. Both DS and dietary ingredients are required to be produced using Good Manufacturing Practices (GMP) and cannot be misbranded or adulterated/contaminated under the DSHEA and other FDA regulations [1]. The Federal Trade Commission (FTC) also has oversight over DS, particularly with respect to advertising and health claims.

Use of DS has increased since the 1970s [4]. According to recent surveys, over half of American adults take at least one DS, with usage increasing with age [5-7]. DS consumers are more frequently women, non-Hispanic white and non-Hispanic Asian, leaner/healthier (lower, normal body mass index [BMI]), educated, and economically stable, viz., higher income [5,6]. Multivitamin-mineral (MVM) products are the most commonly consumed DS. While the reasons for use are multiple, ranging from improved aesthetics (e.g., weight loss, hair, nails, and skin) to enhanced exercise performance, the most often cited reason is for purposes of improving overall health and wellness [5,6,8].

About one third of adolescents also take at least one DS, with MVM products again being the most common [9,10]. Similar trends to adults have also been noted among adolescents, with use more frequent among females, non-Hispanic white and non-Hispanic Asian, lower BMI, and higher family income [10]. In contrast to adults, DS use among children decreases with increasing age, from ages 0 through 19, and may be due to management of oneself,

rather than parents making all decisions for children when they are younger. The main reasons cited for dietary supplementation use among adolescents are to improve/maintain health and to fill specific nutritional gaps.

Role of healthcare providers

Considering the prevalence of DS use, healthcare providers should be aware of which products their patients are taking in order to best manage their overall care. Unfortunately, multiple studies have found that as little as one third of DS users disclose to their primary care physician what they specifically self-administer, especially as related to complementary and alternative medicines (CAMs) (e.g., supplements, acupuncture, meditation) [11-13]. Similar disclosure rates were reported within hospital settings for both inpatients and outpatients [14-16]. For example, only half of users with chronic illness reported DS use to their physicians [12]. This lack of disclosure is not solely related to problems with patients purposely withholding information, as multiple studies have pointed to the lack of inquiry by physicians, in addition to patients not recognizing the pertinence of disclosure, and communication barriers [11,14,15]. However, some patients do believe that their physician will not support their use of DS and many patients cite their lack of reporting due to the belief that the physicians were not well-informed about supplements [11,17]. Interestingly, DS usage among physicians and nurses is reportedly higher than in the general population, 72% and 89% respectively [18], suggesting that these healthcare providers are at least familiar with these products. In fact, approximately 80% of physicians and nurses report recommending DS, highlighting the general support for patient use of these products.

Through patient and physician interviews, it has been determined that dietary supplement discussions that do occur often focus on how the DS are taken and why [17]. However, when asked about DS discussions, both patients and physicians agreed that drug interactions and adverse events should be included and that physicians should also weigh in on the potential benefits.

Unfortunately, due to the vast array of DS currently available, physician knowledge of the specific effects of these products is often very low and likely limited by their own training [17,19]. At least half of physicians were unaware of a reliable resource on DS [20,21] despite many being available [22]. It has been suggested

that physicians' DS knowledge could be increased through continuing education courses, as well as (online) curriculum for those still in residence [23]. If so, it is imperative that the workshops be delivered by someone with a great deal of expertise in this area. For an example, please see: Alternatively, physicians can locate information on DS online through a variety of reliable sites. For example, the U.S. National Institutes of Health featured webpages offer resources such as DS datasheets and a Dietary Supplement Label Database (DSLDB); these include the Office of Dietary Supplements (ODS), National Center for Complementary and Integrative Health (NCCIH), National Library of Medicine, and NIH Health Information [24]. Drug-drug interaction databases such as Micromedex and Integrative Therapeutics can also assist physicians in identifying when DS should not be used. However, it has been noted that due to differences in algorithms, these programs may disagree in their interaction identifications [25]. DS certified by third-party quality verification programs may help guide physicians and consumers in the use of safer products; however, methods and standards differ between programs, and over half of physicians were uninformed about them [20,23]. In cases where physicians are unable to provide enough information on DS, it is important that they direct patients to alternative resources, such as consulting with a well-informed pharmacist or registered dietitian, while keeping the dialogue for future DS discussion open.

Prescription drug and dietary supplement interactions

Nearly two-thirds of DS users take at least one prescription medication [27]. DS can be used to complement and enhance the actions of traditional medicine [28-30]. The effects of cyclosporine, for instance, may be increased by many DS including berberine, cannabidiol, chamomile, grapefruit juice, peppermint, and resveratrol [31,32]. DS can also counteract some of the untoward effects of certain medications. For example, many patients who use statin medication (HMG-coA reductase inhibitors) experience myopathy and associated problems. In such cases, supplementation with reduced co-enzyme Q10 (co-Q10) can alleviate symptoms [33].

While DS can help in some cases, certain DS are contraindicated when considered in conjunction with prescribed medications. For cyclosporine as an example, these include St. John's wort, ginger, licorice, scutellariae radix, and quercetin [32]. DS can interact with prescription medications in two ways: through complementing or opposing the effects of drugs (pharmacodynamics) or by altering

drug absorption and transport (pharmacokinetics) [34]. Identification of DS-drug interactions is hampered by the differences in regulations between DS and prescription medications. Often research of DS-drug interactions are identified by associating DS with specific drug metabolizing enzymes, such as cytochrome P450 enzymes (CYPs) and permeability glycoprotein and then inferring which drugs could be affected. Further, *in vitro* studies generally do not correspond well with *in vivo* results, making human studies and clinical trials more of a necessity [35]. Previous research has involved small studies and case reports that at times have been inconclusive [36]. Further, these studies do not address differences that might occur between subpopulations [37].

An estimated 23,000 emergency department visits a year in the United States are attributed to adverse events from DS [38]. The co-ingestion of DS and prescription medications may lead to additional hospital visits. In survey data from 2011, it was noted that 9.4% of older American respondents were identified as having DS-drug interactions [39]. With the increasing use of dietary supplements in recent years, it would not be surprising if this number was higher today. In a study with 458 DS users who were hospitalized in Israel, researchers identified 15% with “potential clinically significant” DS-drug interactions and up to 47% with at least one possible interaction [40]. These findings reinforce the necessity for physicians to be aware of their patients’ DS use and take an active role in determining their suitability alongside prescription drugs. Herein, some DS-drug interactions and possible interactions are highlighted for common health conditions.

DS Use and DS-drug interactions in autoimmune diseases

Many studies have examined the frequency of DS and other CAMs used among those with an autoimmune disease. DS CAMs (e.g., herbal products, probiotics, vitamins) are frequently used among people with irritable bowel disease (IBD) [41]. As older patients with IBD are more likely to be treated for comorbidities, they are at a greater risk of DS-drug interactions [31]. Over two-thirds of people with multiple sclerosis reported taking vitamins and minerals and a third reported using a natural product [42]. Similarly, almost two-thirds of people with (self-reported) arthritis reported taking a dietary supplement, with 15% using a DS for joints or arthritis [43]. For systemic lupus erythematosus, half of diagnosed patients reported using CAMs [44].

In IBD, thunder god vine (when taken at high doses) can act as an immunosuppressant and improve the efficacy of immunosuppressive drugs [31]. However, there are many serious side effects that have prompted some to not recommend its use [45]. Other herbs used for IBD can adversely interact with drugs. Both chiretta and boswellia act as immunostimulants that may interfere with azathioprine, 6-mercaptopurine, and corticosteroids such as prednisone [31]. While devil’s claw has no known drug interactions, it may increase the serum levels of some drugs through interactions with ATP Binding Cassette Subfamily B Member 1 (ABCB1)/permeability glycoprotein [46]. Ginger may also interact with some drugs [31].

Common DS for rheumatoid arthritis (RA) include fish oil, cat’s claw, rose hip, andrographis paniculate, ginger, willow tree bark, glucosamine, vitamins, and selenium [45]. Few DS-drug interactions are reported for DS and drugs taken for RA. Rather, interactions are more likely to arise from DS for RA interacting with drugs taken for comorbidities such as CVD, depression, and diabetes.

DS use and DS-drug interactions in cancer

The prevalence of DS use among cancer survivors poses the risk of DS-drug interactions [47]. According to one study, the three main reasons for DS use among cancer survivors were to help themselves, boost their immunity, and increase their energy. A few studies have identified cancer survivors/patients with potential DS-drug interactions [48-50]. While many of the DS used to negate side effects of cancer treatments may interact with other prescription drugs, only those associated with chemotherapy are discussed in this section.

Many DS, particularly herbal products, have been shown to interfere with chemotherapeutics. One small study noted that echinacea had no effect on the pharmacokinetics of docetaxel [51]. However, one instance of an adverse interaction with echinacea and etoposide has been documented [22]. Garlic has been found to decrease concentrations of drugs transported by permeability glycoprotein, such as doxorubicin, and may cause toxicity from docetaxel [22,51]. Green tea extract prevents the actions of bortezomib and makes tamoxifen and irinotecan more toxic [52]. Due to alterations to immune response and chemotherapy, Reishi mushrooms may also be contraindicated for cancer patients [52]. Finally, St. John’s wort can decrease the activity and level of docetaxel, irinotecan, and imatinib [51].

DS use and DS-drug interactions in cardiovascular diseases (CVD)

In one study, one in five hospital patients taking at least one cardiac medication were also taking a DS [53]. Among these patients, 90% had an identified DS/medication interaction as determined by the Natural Medicines Comprehensive Database. Unsurprisingly, the study also demonstrated that the risk of DS-drug interactions increases as the number of DS and drugs increase. Therefore, physicians need to be more vigilant monitoring DS and adverse effects in patients on multiple medications.

Many DS have been identified that may interfere with a variety of drugs that are used in the management of CVD. For example, cranberry, ginseng, ginger, and *Salvia miltiorrhiza* can all increase bleeding risk when taken with warfarin [22,54]. Garlic and ginkgo are generally not recommended to be used with anticoagulants or aspirin [54]. European Elder increases the effect of diuretics, while combining licorice root with some diuretics can result in low potassium levels. Black cohosh may reduce the effects of statins, and in one case, increased liver enzymes when taken with atorvastatin [22]. Niacin should also not be taken with statins due to potentially severe adverse effects (e.g., rhabdomyolysis, renal failure) [39]. Finally, hawthorn should not be taken with digoxin [54].

DS use and DS-drug interactions in diabetes

A Polish survey of 150 adults with Type II Diabetes Mellitus found that half used DS [55]. The DS ranged from minerals, to MVMs, to herbs. The researchers concluded that the use of DS along with poor nutrition placed patients at risk for drug interactions. Researchers also found that a third of respondents had dyslipidemia and half had CVD. This could indicate additional adverse effects from DS due from comorbidities, as well as other possible DS-drug interactions from additional drugs.

Many dietary supplements can interfere with the effectiveness of diabetic medications by causing hyperglycemia (e.g., niacin, fish oil, St. John's wort) or hypoglycemia (e.g., chromium picolinate, flax seed, ginger, ginseng, yohimbe) [56]. Both horse chestnut seed and licorice interfere with insulin, which could cause hypoglycemia and hypokalemia, respectively. Finally, taking magnesium citrate and sulfonyleureas together may result in sodium imbalances.

DS use and DS-drug interactions in neurological conditions

In three separate surveys of patients with epilepsy, approxi-

mately one half of patients reported taking a DS [57-59]. The DS were mainly vitamins and minerals and were taken primarily for general health. One study found that 27% of subjects were taking medication for a condition other than epilepsy, and nearly 10% of patients were taking herbs that were either pro-convulsive (e.g., *Ginkgo biloba*, evening primrose oil, *Hypericum perforatum*) or had possible DS-drug interactions (Ginseng) with either epilepsy or SSRI medications [58]. A second study found that 54% also had a comorbidity [57]. As previously described, this could lead to additional DS-drug and drug-drug interactions. In a study of people diagnosed with Parkinson's Disease, 63% of patients were taking a dietary supplement, with 54% of survey participants taking vitamins and only 7% using an herbal product [60].

While many drugs themselves are neurotoxic or may induce epilepsy, some DS specifically have DS-drug interactions with anti-epileptic drugs. Grapefruit juice increases the effectiveness of carbamazepine and diazepam [61]. Ayurveda and milk thistle decrease serum levels of phenytoin [22,61]. Ginkgo decreases the availability of phenytoin and valproate [61].

DS use and DS-drug interactions in retroviral diseases (HIV/AIDS)

In a London survey of 293 HIV patients, 61% reported using a dietary supplement [62]. According to a 2012 report, one in four HIV patients were taking a DS other than MVMs, with the most common being antioxidants and teas followed by herbal products [63]. DS can enhance or attenuate retroviral treatment by inhibition or induction of CYP3A4, respectively [64,65]. DS can be used to enhance retroviral treatment as well as alleviate symptoms. At least two DS (primrose oil and cat's claw) have been shown to increase blood levels of retroviral drugs [64]. DS that may induce CYP3A4 include garlic, ginkgo, ginger, milk thistle, St. John's wort, and vitamin C. St. John's wort also decreased levels of Indinavir and Nevirapine. However, studies with ginger showed no effect and the findings for garlic, ginkgo, and milk thistle are inconsistent. Vitamin C was also found to decrease the efficacy of Indinavir. Additionally, minerals (e.g., calcium carbonate, ferrous fumarate, and zinc sulfate) as well as MVMs are suspected of chelating some retroviral drugs, decreasing their effectiveness. While *Sho-seiryu-to/sho saiko-to*, a botanical mixture used in traditional medicine, does not directly interact with carbamazepine, it increases levels of the drug [61].

Other example DS-drug interactions

Both goldenseal and St. John's wort are generally not recommended to be taken with prescription medications or over the counter medications [22]. Ginseng may interact with anti-depressants. Echinacea and Curcumin may interfere with anti-psychotics and anti-depressants. Echinacea should also be avoided prior to general surgery that uses the sedative Midazolam [51]. Similarly, ashwaghandha (Indian ginseng, poison gooseberry, winter cherry) decreased the efficacy of Triazolam, a sedative, and should be avoided for general surgery when Triazolam is used [52].

Reporting of DS adverse events

Whether taken alone or with prescription medications, DS-related adverse events should be reported. The FDA relies on consumers and physicians to report adverse effects that are thought to be associated with a DS through the Safety Reporting Portal, found here: <https://www.safetyreporting.hhs.gov> [66]. The FDA describes what is considered a serious reaction on its website. According to a 2013 study, in the military where DS use is prevalent, 60% of physicians believed they had observed adverse DS effects, but only 18% reported it [21]. Similar findings were reported by sports medicine physicians, with 71% observing, but only 10% reporting DS linked adverse effects [20]. Compared to the estimated emergency room visits due to DS, the number of adverse events reported by consumers is extremely low (an average of 400 per year between 2011 and 2013) [67]. Over a 9-year period, FDA Med-Watch released less than 25% of the regulatory alerts as compared to Health Canada [68]. Underreporting adverse effects could lead to unsafe DS remaining on the market longer and potentially causing harm to additional consumers.

Practical applications

In order for a medical provider to assess whether a supplement is appropriate for a patient, they need to determine whether use of a DS is scientifically supported by clinical trials, whether the dosage is appropriate, whether it may interact with a patient's current medical regimen, and whether the supplement source itself is safe. Two hypothetical examples are provided to highlight the complexity of co-use of multiple DS and prescription medications.

CVD with statin therapy and Co-Q10

A customer at a retail pharmacy asks a pharmacist their opinion about the use of co-enzyme Q10, as a method of reducing their

statin-induced myopathy. The customer has been experiencing muscle pain and weakness since starting on statins and read that co-Q10 might help. As Co-Q10 is one of the most popular DS, the pharmacist is familiar with the product [69]. The pharmacist asks the customer about their current health conditions and medications they are taking other than the statin, as she understands that Co-Q10 may interfere with warfarin and insulin but is otherwise safe [70]. The customer claims that he is taking only the statin, along with seasonal allergy medication. The pharmacist states that she would recommend a dosage of 200-300 mg per day and highlights the use of reduced Co-Q10 (ubiquinol) over ubiquinone, due to the much better absorption of the former [71-73].

Type II diabetes wanting to add DS to management regimen

Upon asking about their DS use, a patient with poorly-controlled Type II diabetes mellitus discloses to their general practitioner (GP) that, while they are not currently using any DS, they have considered adding a specific DS to their current treatment regimen of metformin and insulin, in an attempt to assist with lowering their blood sugar. The GP, before even addressing the question of dietary supplement use, stresses to the patient the importance of regular physical activity and exercise, as skeletal muscle contraction will help to manage blood sugar [74]. Moreover, he stresses the importance of dietary modification, as this is of crucial importance for all diabetics [75]. Referrals to an exercise physiologist and registered dietitian, respectively, would be the best course of action in this case.

Beyond the above, if the GP is unfamiliar with the DS, he might first use the DSLD to ascertain the supplement ingredients (cinnamon extract, chromium, resistant starch, vinegar), as well as the amount of each constituent. The GP could then use datasheets available from the ODS to find that cinnamon is not currently supported for the management of diabetes [76], although individual studies have found specific cinnamon extracts might prove helpful in managing blood sugar [77-79]. The GP could also find that on the chromium datasheet, it is not recommended for diabetes management and that there may be interactions between chromium and certain drugs [80]. Through a general literature search (e.g., Pubmed, Google scholar), the GP might find a meta-analysis noting that resistant starch could be beneficial to individuals who are overweight and have diabetes [81]. The GP might also find a review on vinegar, that recommends its use for diabetes [82]. The DS might

therefore help lower blood sugar, but the patient would need to actively monitor their glucose, as adding it to the prescription medications, in particular if they begin an exercise program and modify dietary intake favorably, could lead to hypoglycemia.

This example demonstrates that DS information can certainly be found, but it may require extensive research from multiple sources and may not yield complete/or decisive recommendations. Further, although the patient is asking about a supplement to manage diabetes, there may be complications with other existing health conditions they may have or medications they are taking. Physicians and their patients must be aware of other considerations, such as the following: while DS labels are required to include both the ingredient components and their amounts, past research has found that they are not always accurate on either account. Adulteration with prescription drugs, contamination, and higher than reported levels of ingredients, especially when multiple DS with overlapping ingredients are concomitantly taken, may result in adverse effects [83-85].

Conclusion

Physicians and other healthcare providers should be an important resource for patients seeking to use DS. Despite the high rate of DS use among the general population in the United States, the rate of DS disclosure to physicians is low. This impedes the ability of physicians to advise patients on the efficacy of their use and, more importantly, prevents them from identifying serious adverse reactions that may and do occur. Physicians and other healthcare professionals require additional training specific to DS supplements and need to be made aware of the multiple resources that are already available to them. More knowledge and awareness will help them provide better treatment, which is guided by evidence and not mere speculation. The reality is that many DS can prove helpful to patients. However, there exist many more that have little evidence of effect and may actually prove harmful if taking in conjunction with prescription medications.

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