Safety and Efficacy of Dietary Supplements for Diabetes

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Results from various surveys show that 30–70% of adult people with diabetes in the United States use alternative medicine, with one-third using it specifically to improve diabetes-related symptoms (1). Individuals with diabetes may be inclined to use these products for various reasons, including a belief that "natural" means without risks, concern over medication costs, influence from family and friends, and desire for further glucose lowering in addition to that achieved with traditional medications. However, supplements have the potential to cause adverse effects, drug interactions, and toxicity. Additionally, lack of regulatory oversight in the manufacturing and marketing of supplements can lead to inconsistent quality and quantity of ingredients within products.

Randomized controlled trials (RCTs) are essential for assessing safety and efficacy of therapeutic interventions. However, there are a limited number of RCTs for supplements, and conclusions are often derived from studies of weak quality. For many dietary supplements, data are lacking on important information such as mechanisms of action, pharmacokinetics, and potential toxicity. The desired clinical outcome may be dependent on the mechanism of a supplement, which may affect insulin secretion, affect insulin resistance, or have multiple effects (2). The selection of a supplement might also depend on other factors, including stage of diabetes, comorbidities, and availability.

There may be inconsistencies in the reconciliation of dietary supplements, which could result from individuals choosing to not disclose information on their use of supplements, providers not asking about such use, or a lack of recording such information in the medical record. In one study of 333 hospitalized patients who self-reported dietary supplement use, 20% were asked about the use of dietary supplements by the health care professional during their stay, and only 6% of all supplement users were asked, disclosed, and had documentation (3). Therefore, it is important for health care professionals to encourage open communication with patients and to educate them on the evidence behind the use of alternative medicines.

Regulations

In 1994, the dietary supplement market underwent a major change as a result of legislation called the Dietary Supplement Health and Education Act (4). Under this regulation, supplements are now regulated under the umbrella of "foods." Whereas the manufacturer of a prescription drug product must conduct research to determine both safety and effectiveness before the medication reaches the market, dietary supplements can be marketed without submitting safety data. Manufacturers are required to create their products following laws established for good manufacturing practices. Although the U.S. Food and Drug Administration (FDA) has the authority to conduct random inspections of facilities and products, limited resources and the production of high volumes of supplements pose challenges for routine monitoring. In addition, many ingredients are sourced from other companies.

Manufacturers are responsible for ensuring that their product labels and ingredient lists are accurate. If a manufacturer makes a structure or function claim on a dietary supplement label, a printed disclaimer is required by law. It should state that the claim has not been evaluated by the FDA and that the product is not intended to "diagnose, treat, cure, or prevent any disease" (5). The FDA must prove that a supplement is unsafe before it can be removed from the market. Therefore, supplements could be adulterated or counterfeit or could contain unapproved medications.

Supplements

Many supplements have been studied for the treatment of diabetes (Table 1). However, most have limited data on efficacy and some carry potential risks in certain patient populations. Individuals should be directed to

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TABLE 1 Supplements for Diabetes

	Studied Dose	Safety*	Efficacy*	Comments
α-Lipoic acid	300–1,800 mg daily PO	Possibly safe SE: GI upset, headache, skin rash	Possibly effective	May decrease effectiveness of thyroid hormone
Berberine	0.9–1.5 g daily PO	Possibly safe SE: GI upset	Possibly effective	Avoid if pregnant because of uterine stimulant effects; antiplatelet effects; drug interactions (CY P2C9, CY P2D6, CY P3A4)
Bitter melon	2–4 g daily	Possibly safe SE: GI upset, headache, dizziness	Insufficient reliable evidence	Avoid if G6PD deficient because of increased risk of favism
Chromium	200–1,000 μg daily PO	Possibly safe SE: GI upset, headache, mood changes	Possibly effective	Caution if kidney or liver issues present
Cinnamon	120–6,000 mg daily PO	Likely safe Generally well tolerated	Possibly effective	Unsafe in higher doses; caution if taking warfarin or liver issues present; drug interactions (CY P2C9, CY P3A4, CY P2A6, CY P2D)
Fenugreek	5–100 g daily PO added to 1–2 meals/day	Possibly safe SE: GI upset	Possibly effective	Avoid if pregnant due to uterine stimulant effects
Flaxseed	10–60 g daily PO	Likely safe SE: GI upset	Possibly effective; effects highest with whole flaxseed	Caution with hormone-sensitive cancers (e.g., breast cancer)
Ginseng	3,000–9,000 mg PO up to 2 hours before a meal; no added benefit found to taking >3,000 mg	Likely safe SE: headaches	Possibly effective	Avoid if taking warfarin
Gymnema	250–500 mg twice daily	Possibly safe SE: drug-induced hepatitis (rare)	Insufficient reliable evidence	Drug interactions (CY P1A2, CY P3A4, CY P2C9)
Ivy gourd	1–20 g daily	Possibly safe SE: none reported	Possibly effective	Insufficient reliable information available on toxicology
Prickly pear cactus	300–500 g daily	Possibly safe SE: GI upset	Possibly effective	Usually studied as single doses; unknown whether extended daily use can lower glucose levels

*Ratings published in the Natural Medicines database (https://naturalmedicines.therapeuticresearch.com). G6PD, glucose-6-phosphate dehydrogenase; PO, orally; SE, side effects.

noncommercial resources to find reliable information (Table 2). It is important to assess efficacy, potential side effects, and the design of the clinical trials when evaluating the appropriateness of a therapy. For example, specific medication formulations (e.g., whole flaxseed versus flaxseed oil) and patient populations (e.g., individuals with diabetes and chromium deficiencies) may have been studied. In addition, health care professionals should check for potential medication interactions when patients report supplement use. Many supplements are metabolized by cytochrome (CY) P450 enzymes and could potentially result in additive side effects or reduced efficacy of other medications.

α-Lipoic acid (ALA) is an antioxidant that may reduce fasting blood glucose (FBG) levels and improve insulin sensitivity in patients with type 2 diabetes, but it does not significantly lower A1C (6–8). It has not been shown to benefit individuals with type 1 diabetes. ALA appears to be generally well tolerated when taken orally for up to 4 years but may cause gastrointestinal (GI) upset, mild rash, and headache (9). In addition, it may decrease the effectiveness of synthetic thyroid hormone (10). ALA has been studied for diabetic neuropathy at a dose of 600–1,800 mg daily, although a person may have to take it for 3–5 weeks before noticing an improvement (11).

TABLE 2 Resources for Supplement Information

Organization	Website	Mobile App Available?	Comments
Natural Medicines*	https://naturalmedicines.therapeuticresearch.com	Yes	Up-to-date information and drug interaction checker
Memorial Sloan-Kettering Cancer Center: About Herbs, Botanicals & Other Products	https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs	Yes (*About Herbs*)	Up-to-date information
Epocrates*	https://www.epocrates.com	Yes	Drug interaction checker includes supplements
Medscape	https://www.medscape.com	Yes	Drug interaction checker includes supplements
MedlinePlus, National Library of Medicine	https://medlineplus.gov	No	General information for supplement users and health care providers
National Center for Complementary and Integrative Health, National Institutes of Health	https://nccih.nih.gov	Yes (*HerbList*)	General information for supplement users and health care providers
Office of Dietary Supplements, National Institutes of Health	https://ods.od.nih.gov	No	General information for supplement users and health care providers
U.S. FDA	https://www.fda.gov/food/information-consumers-using-dietary-supplements/tips-dietary-supplement-users	No	Tips and a handout for dietary supplement users
U.S. FDA	https://www.fda.gov/food/food-labeling-nutrition/label-claims-conventional-foods-and-dietary-supplements	No	Information on label claims for conventional foods and dietary supplements

*May require product purchase or paid subscription fees.

Research into **bitter melon** has yielded conflicting results in small and short-term clinical studies. Several mechanisms of action have been proposed, including inhibition of intestinal absorption of glucose and decreased hepatic gluconeogenesis (12). One trial showed that taking bitter melon extract 3 g daily for 3 months did not lower A1C or fasting plasma glucose (FPG) compared with placebo in patients with newly diagnosed or poorly controlled type 2 diabetes (13). In this study, capsule preparations were generally well tolerated, but GI complaints such as abdominal discomfort and diarrhea were the most commonly reported adverse events. A meta-analysis showed that consumption of bitter melon 1–6 g daily for 4–12 weeks does not significantly improve FPG or A1C compared with placebo (14). However, another study looking at a component of bitter melon called compound K16 showed that it can upregulate the expression of insulin signaling pathway–associated proteins (15). More evidence is needed to confirm the effectiveness of bitter melon for use in diabetes.

Berberine has been studied at a dose of 0.9–1.5 g orally per day (11). A meta-analysis showed that it may decrease FPG and postprandial glucose (PPG) by 15 and 34 mg/dL, respectively, and A1C by 0.7% when compared with lifestyle interventions alone (16). Berberine should be avoided in pregnant women because it may cause premature contractions and fetal brain damage (17). It may also increase the risk of bleeding if used with agents such as warfarin or aspirin because of its antiplatelet properties (18). Additionally, it is important to consider the potential for supplements to affect the metabolism of other medications. Berberine has been shown to affect CY P450 P2C9, P2D6, and P3A4 enzymes (19).

Chromium may increase insulin sensitivity and lower A1C by up to 0.6% and fasting blood glucose by up to 18 mg/dL (20). It may also reduce weight gain in patients already on a sulfonylurea. Some studies have shown no clinical benefit with the use of chromium, whereas others have only seen efficacy in people with poor nutritional status or low chromium levels. One of the largest studies that found benefit enrolled patients in China, where poor nutritional status was more likely (21). The FDA and Institute of Medicine suggest that it is safe when taken at a dose of 200 μg daily for up to 6 months. However, there are some

case reports of chromium causing both renal and liver injury (22,23).

Cassia cinnamon is possibly effective in lowering blood glucose levels but should be used in moderation (24). Cinnamon spice sold in stores may contain a combination of different types of cinnamon, but cassia is the most common cinnamon sold in the United States. Adding cassia cinnamon to a patient's diet has been shown to reduce FPG by an average of 25 mg/dL (25). It has a Generally Recognized as Safe rating from the FDA when used orally and appropriately long term. Cassia cinnamon may increase levels of coumarin, which has blood-thinning properties, and lead to liver impairment at higher doses (26). It may also potentially affect the activity of CY P2C9 and P3A4 enzymes (27).

Fenugreek is an herb that may decrease FPG and PPG by 15 and 23 mg/dL, respectively, and A1C by 1.16%, as seen in one meta-analysis of 10 clinical studies (28). However, dosages and formulations were not uniform across the trials. Preparations included powder, seeds, and capsules and varied in the methods of herbal processing (e.g., debitterized, defatted, and deodorized; roasted and converted to powder; and alcohol extraction). Evidence shows that it is possibly safe when used orally for up to 6 months (29). Mild GI symptoms such as diarrhea and flatulence are the most common side effects, especially when taken on an empty stomach (29). It has potential uterine stimulant effects and so should be avoided in pregnant women (30). In addition, fenugreek contains coumarin that could cause antiplatelet effects, but this does not appear to be a common clinical outcome (31).

Flaxseed has been studied at a dose of 10–60 g orally per day for up to 48 weeks (32). Whole flaxseed has been shown to reduce insulin resistance and improve insulin sensitivity, resulting in an average blood glucose reduction of 6 mg/dL with no change in A1C (33). Its effects seem to be greatest with consumption of whole flaxseed rather than flaxseed oil. There is some evidence that the oil contained in flaxseed can decrease platelet aggregation (34). Side effects include GI upset such as bloating and flatulence (35,36). Because of its potential estrogenic effects, patients with estrogen receptor–positive breast cancer should use this supplement with caution (37).

Ginseng is available in different types such as Asian ginseng (panax ginseng) and American ginseng (panax quinquefolius). American ginseng has been reported as the most studied and safe type of the supplement (38). It is safe to take up to 3 g for 12 weeks and may potentially lower FPG by 16 mg/dL with no change in A1C (39). No study has shown added benefit to taking more than 3 g daily. It is important to advise patients taking warfarin to not take American ginseng, which can decrease the effectiveness of warfarin (40).

Gymnema, also known as gurmar, is an herb that grows in the tropical regions of India and Africa. An open-label study conducted in 58 patients with type 2 diabetes investigated the effects of gymnema leaf extract 250 mg twice daily for 3 months compared with placebo. Individuals given the extract showed statistically significant improvements in FBG by 26 mg/dL and A1C by 1% (41). In another trial, administration of gymnema extract 500 mg twice daily for 60 days resulted in a decrease in mean FPG and PPG by 43 and 55 mg/dL, respectively (42). No side effects have been reported with its use.

Ivy gourd is a plant that grows in many parts of India and appears to have insulin-mimetic properties. In one double-blind trial of 61 healthy volunteers, a meal containing 20 g of ivy gourd leaves was administered to participants. There was a statistically significant mean difference in PPG of 11.46 mg/dL between the experimental and control groups (43). In an RCT of 60 patients with type 2 diabetes, FPG and PPG decreased by 16 and 18%, respectively, after taking 1 g daily of ivy gourd extract for 90 days (44). No adverse events were reported in these trials. The preliminary evidence suggests that there is a potential role for ivy gourd in individuals with diabetes.

Prickly pear cactus is primarily used in Mexican cultures as a treatment for type 2 diabetes. It has a high content of soluble fiber and pectin, which may affect intestinal glucose uptake and cause hypoglycemic effects (45). A single dose of 300 g steamed prickly pear cactus when added to a high-carbohydrate meal, but not when added to a high–soy protein meal, may decrease PPG. Another study demonstrated that adding prickly pear cactus to common Mexican breakfast meals could reduce PPG by 20–48% (46). Dehydrated prickly pear cactus leaves have been safely used for up to 2 years at a dose of 15 g daily (47). It is not known whether extended daily use can lower blood glucose and A1C levels.

Other products marketed for diabetes commonly contain a combination of multiple supplements. For example, ingredients in Diabecon include bitter melon and gymnema. It is proposed that this promotes β-cell repair and regeneration, protects β-cells from oxidative stress, and increases C-peptide levels (48). As mentioned previously, these supplements are potentially safe but currently have insufficient reliable evidence in people with diabetes (13–15,41,42). One meta-analysis showed that supplementation with probiotics significantly reduces glucose levels and improves insulin resistance (49). However, more RCTs with larger

sample sizes and consistency with regard to product ingredients are needed to confirm these findings.

Discussion

There may be several challenges to ensuring that supplement users receive appropriate information from their health care providers with which to make sound health decisions. One reason is that providers may have limited training and knowledge about dietary supplements. In one study that assessed the baseline knowledge of 335 physicians on alternative medicine, one-third were unaware that supplements did not require FDA approval or submission of safety and efficacy data before being marketed (50). Thus, it is important for health care providers to be educated on the regulations surrounding the use of dietary supplements. Another potential challenge is the limited amount of time available to discuss supplements when multiple problems are commonly addressed during physician visits (51). However, the use of supplements should be treated in a similar manner to the use of traditional therapies. Patients may choose to not disclose their supplement use because they anticipate a physician's negative response or inability to contribute beneficial information, perceive that alternative therapies do not affect traditional treatments, or hold personal beliefs about the appropriate coordination of care (52).

Effective communication skills are crucial during a shared decision-making process between patient and provider to assist in creating a consensus approach on the best clinical course. Simply asking about supplement use in an open, nonjudgmental way is an important step to assessing the use of alternative medicines. Giving patients permission to discuss the topic and their perspective and beliefs can aid in keeping communication open (53). It is important that health care providers respect patient autonomy and provide information about the evidence on efficacy and risks of supplements and how alternative therapies compare with traditional therapies. Discussing supplements does not mean that a health care provider is endorsing or promoting their use. Rather, reviewing patients' treatment preferences and expectations and supporting their efforts to obtain answers to important questions about alternative therapies can help providers and patients identify a mutually acceptable course of action.

Conclusion

Individuals may consider supplements to be without risks because they are "natural." However, concerns regarding the use of supplements include potential drug interactions, increased risks of hypoglycemia and other adverse effects, inconsistent quality and quantity of supplement ingredients, and delays in the initiation of therapies shown to improve clinical outcomes. Current regulations prevent the FDA from investigating supplements with respect to safety, efficacy, or marketing claims before they are sold to consumers. It is therefore important that health care providers initiate discussions of the use of supplements and provide evidence-based, patient-centered care with regard to their possible use.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

L.V.C. researched data, wrote the manuscript, and reviewed/edited the manuscript. J.R.T. researched data, contributed to discussion, and reviewed/edited the manuscript. L.V.C. is the guarantor of this work and, as such, takes responsibility for the integrity of the data presented and the accuracy of the data analysis.

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