In Brief

Individuals with diabetes are more likely than those without diabetes to use different modalities that may not be considered part of mainstream allopathic or conventional medicine. Many dietary supplements of botanical and nonbotanical origin are available over the counter to treat diabetes or its comorbidities. Clinicians must maintain a respectful attitude toward patients' health care values and beliefs, encourage open dialogue, and provide accurate, nonjudgmental information about different supplements. It is essential that clinicians stay informed about dietary supplements to evaluate whether side effects or potential interactions among medications, dietary supplements, medical conditions, or nutrients may occur.

Dietary Supplements for Diabetes: An Evaluation of Commonly Used Products

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The Dietary Supplement Health and Education Act (DSHEA) enacted in 1994 established the definition of "dietary supplement" as "a product taken by mouth that contains a 'dietary ingredient' intended to supplement the diet." The dietary ingredients in these products may include minerals, vitamins, herbs or other botanical ingredients, amino acids, and substances such as enzymes, organ tissues, and metabolites.[1] DSHEA categorizes dietary supplements under the general umbrella of "foods" rather than drugs and requires that every product be labeled as a dietary supplement.[1] These products are available in a variety of dosage forms.[1]

Patients use many products and modalities to treat diabetes or its comorbidities. People with diabetes are 1.6 times more likely to use a complementary and alternative medicine (CAM) treatment modality than those without diabetes.[2] CAM includes acupuncture, reflexology, massage therapy, chiropractic services, and biological complementary therapies, which include dietary supplements.[3] Individuals who use dietary supplements may believe such use allows them to maintain control of their own care. Patients often believe dietary supplements are not drugs and have fewer side effects than conventional medications.

Clinicians also should be aware that one-third of individuals with diabetes may use some of these unique modalities.[4,5] Despite the fact that dietary supplement use is common, only 33.4% of individuals using herbal products and dietary supplements inform their conventional health care providers about such use.[6] Nevertheless, dietary supplements may cause side effects or interactions with prescription or over-the-counter drugs or with other supplements or even nutrients.

This article lists some of the commonly used products, presents background information and clinical studies, and summarizes issues regarding potential side effects and drug interactions for each product. Frequently used products for diabetes include aloe vera, bitter melon, chromium, cinnamon, fenugreek, ginseng, gymnema, milk thistle, nopal, salacia, and salvia.

Aloe (*Aloe vera L*)

Aloe is a member of the *Liliaceae* family and grows well in warm climates. Aloe gel is a clear substance harvested from the core of the leaf after the main stalk has been cut away. Aloe gel has been used to treat diabetes and hyperlipidemia, but another plant component, dried aloe leaf juice, was previously found in over-the-counter laxative formulations.[7] Aloe is popular in capsule or tablet form all over the world and is also available in liquid form. Hispanic patients have used *sábila* (aloe) in shakes and smoothies.

Two 6-week studies by the same researchers published consecutively in the journal *Phytotherapy* reported on aloe use in diabetes. One study was

a single-blinded, placebo-controlled study in patients newly diagnosed with type 2 diabetes.[8] Forty patients received one tablespoonful of aloe gel or placebo twice daily for 6 weeks. Fasting glucose declined from 250 to 142 mg/dl in the aloe group (P = 0.01). The other 6-week trial was a single-blinded, controlled trial in 40 patients with established type 2 diabetes. Aloe gel (one tablespoonful twice daily) or placebo was taken with a sulfonylurea.[9] Fasting glucose declined significantly from 288 to 148 mg/dl (P = 0.01 vs. control). In each of these trials, triglycerides also decreased significantly by ~ 50% (P = 0.01).

In an uncontrolled study of five patients with type 2 diabetes, one-half teaspoonful twice daily of dried aloe sap (administered for 4–14 weeks) resulted in a mean A1C decrease from 10.6 to 8.2% (P value not reported).[10] Mean fasting glucose decreased from 273 to 151 mg/dl ($P < 0.001$).

Aloe contains glucomannan, and the increased fiber may account for the mechanism of action—glucose uptake.[7] Adverse effects, including electrolyte depletion, have been reported for the laxative form.[7] A case report of prolonged bleeding when used with certain general anesthetics during surgery warrants discontinuation of aloe 1–2 weeks before surgery.[11] Short-term use may decrease fasting glucose and possibly A1C.

Bitter Melon (*Momordica charantia*)

Bitter melon is a plant also known by other names such as bitter gourd, karela, balsam pear, or Ampalaya tea. It is related to honeydew melon and cantaloupe and is consumed as a vegetable in countries such as India and Asia. The fruit and seeds are the parts thought to help diabetes control.[7,12] Bitter melon has been used for gastrointestinal and dermatological disorders and by women as an emmenogogue and abortifacient, so it is not recommended during pregnancy.[7,12,13]

An injectable "plant insulin" preparation was studied in patients with type 1 or type 2 diabetes and compared to a control group with diabetes.[14] Dosing was based on blood glucose levels. Fasting glucose was measured, and bitter melon was then administered. Glucose was measured several hours after injection. In patients with type 1 diabetes, mean fasting glucose decreased from 304 to 169 mg/dl 4 hours after injection ($P < 0.05$), and this effect was maintained at 6 and 8 hours after injection (176 and 174 mg/dl, respectively, $P < 0.05$ compared to baseline). In the patients with type 2 diabetes, blood glucose did not decline significantly but differed from the control groups at 1 and 6 hours ($P < 0.05$).

A 2-day study was done in 100 type 2 diabetic patients using an aqueous pulp suspension.[15] The authors did not provide doses but stated they were based on body weight. Glucose values declined on the second day.

The first randomized, double-blinded, placebo-controlled study was conducted in 40 adults with newly diagnosed or poorly controlled type 2 diabetes.[16] Patients were instructed to take two capsules (made of 100% dried whole fruit but actual amount not given) of the bitter melon product after meals three times daily for 3 months. In both the bitter melon and placebo groups, A1C increased from a mean baseline of ~ 8%, although the increase was less pronounced in the bitter melon group (0.28 vs. 0.5% increase for bitter melon vs. placebo, respectively; P = 0.4825). Fasting glucose declined from 151.2 to 143.8 mg/dl in the bitter melon group, but the decrease was not significant.

Bitter melon is becoming increasingly popular in the United States. Theoretical mechanisms include insulin-like properties, glucose uptake, decreased hepatic gluconeogenesis, increased peripheral glucose oxidation, and inhibition of enzymes involved in glucose production.[16] Some constituents may also activate adenosine 5´-mono phosphate-activated protein kinase, an enzyme known to facilitate glucose uptake.[17] It may cause low blood glucose when combined with secretagogues.[18]

People of Mediterranean or Middle Eastern descent with known glucose-6-phosphate dehydrogenase deficiency should also avoid its use because of the possibility of favism and hemolytic anemia.[7,12,13] Other people who should avoid the use of bitter melon include children, lactating women, and people with allergies to the melon family.

Dosage forms include juice, powder, vegetable pulp suspensions, injections, and now capsules. Manufacturers have stated that the recommended dose is 3 g/day.[19] Bitter melon is probably safe when consumed as a vegetable, but it may not be consistently safe when used as a supplement. A recent well-designed study reported that a capsule form was not as effective as in previous studies.[16]

Chromium

Chromium has long been a popular agent for diabetes control. Dietary forms include whole grains, green vegetables, meats, nuts, and egg yolks, as well as brewer's yeast and certain beers and wines.[7] Controversy exists because there is insufficient information to establish appropriate chromium body stores, and thus it is difficult to determine if a person is in a deficient state and how much supplementation is required to provide benefit. However, chromium deficiency may occur during pregnancy[20] or when a person has a poor diet, is on total parenteral nutrition, or has poor glucose control.[7,21]

Positive effects of chromium have been shown in type 1, type 2, and gestational diabetes.[21] However, studies show varying effects. A frequently cited trial was done in 180 Chinese patients.[22] In this randomized, double-blinded, placebo-controlled trial, subjects were given placebo, 200 µg/day, or 1,000 µg/day of chromium for 4 months. At 4 months, fasting glucose was 128 mg/dl in the 1,000-µg group ($P < 0.05$ for the 1,000-µg group vs. the other two groups). At 4 months, A1C was 8.5, 7.5, and 6.6%, respectively, in the placebo, 200-µg, and 1,000-µg groups. The A1C decrease was 2.8% in the highest dose group and 1.9% in the other chromium group ($P < 0.05$ decrease for both chromium doses vs. placebo). Overall, effects were dose-dependent and were seen at 2 and 4 months.

A meta-analysis of randomized controlled trials reported that data are inconclusive and more studies are needed to evaluate the role of chromium supplementation in diabetes.[23]

Recent interest in the combination of chromium picolinate with biotin has emerged. Biotin is a water-soluble B vitamin that also plays a role in carbohydrate and lipid metabolism and enhances the effect of chromium on glucose disposal and lipid metabolism. One study demonstrated improved glycemic control when a combination of 600 µg of chromium plus 2 mg of biotin was used in people with type 2 diabetes who were also on oral agents and had an A1C ≥ 7%.[24] The study was a 90-day randomized, double-

blinded, placebo-controlled trial. It included 226 people on chromium and 122 on placebo. Mean A1C declined by 0.54% in the chromium group from a baseline of 8.73% and by 0.34% from a baseline of 8.46% in the placebo group ($P = 0.03$ vs. placebo). Mean fasting glucose also decreased by 9.8 mg/dl in the chromium group ($P = 0.02$ vs. placebo).

Chromium is a trace element that may be deficient in people with diabetes. Controversy surrounds assessment of chromium deficiency. Researchers have suggested that lower toenail chromium concentrations are found in subjects with increased risk of diabetes.[25] Chromium may work as an insulin sensitizer and enhance β-cell function.[7,24] However, studies of chromium in impaired glucose tolerance, type 1 diabetes, and type 2 diabetes have been inconsistent. Although a landmark study done in Chinese patients[22] showed benefit, critics have suggested that results of this study cannot be extrapolated to other populations because the patients were leaner than typical patients with diabetes and differed in dietary chromium intake from average American diets.

Adverse effects have included renal toxicity if used in higher than recommended doses[26–28] or dermatological eruptions.[29] Short-term, dose-related responses have been reported, and although doses up to 1,000 µg/day for 64 months have not resulted in adverse effects,[30] a typical dose is 200 µg/day.[7] Chromium picolinate salt appears to be the most efficacious form.[7] Supplements containing chromium picolinate in combination with biotin are undergoing extensive study, and the dose used is 600 µg/day plus 2 mg daily of biotin.[24] The Food and Nutrition Board of the Institute of Medicine has stated there is insufficient evidence to set an average requirement, and an adequate intake is based on mean intake.[31]

Based on a small study,[32] the U.S. Food and Drug Adminstration authorized a qualified health claim that chromium picolinate may decrease the risk of insulin resistance.[33] The American Diabetes Association's official position is that there is inconclusive evidence demonstrating the benefit of chromium supplementation.[34] Chromium continues to be frequently used, however, and serious adverse outcomes have not been reported.

Cinnamon (*Cinnamomum cassia*)

There are two major types of cinnamon, including *Cinnamomum verum,* or true cinnamon, and *Cinnamomum cassia,* also known as *Cinnamomum aromaticum*.[7,35] The cassia form is used for diabetes.[7,35] Cinnamon comes from an evergreen tree that grows in tropical climates; the bark is removed in short lengths and dried.[7]

One study in 60 Pakistani patients on sulfonylureas with poorly controlled type 2 diabetes found that cinnamon improved glucose and lipids.[36] Patients were given 1, 3, or 6 g/day of cinnamon or placebo for 40 days. Fasting glucose decreased from a baseline of 209 to 157 mg/dl on 1 g/day; use of 3 g/day decreased glucose from 205 to 169 mg/dl, and use of 6 g/day decreased glucose from 234 to 166 mg/dl ($P < 0.05$ for all three groups vs. baseline). Cinnamon was withheld for the next 20 days, and fasting glucose was still lower than at baseline, indicating that cinnamon may have a sustained benefit. Total cholesterol, triglycerides, and LDL cholesterol also declined significantly.

A different randomized, double-blinded, placebo-controlled trial in 65 German patients with well-controlled type 2 diabetes (mean baseline A1C of 6.8%) assessed cinnamon use.[37] Subjects took 112 mg of aqueous cinnamon extract (~ 1 g) or placebo three times a day with meals for 4 months. Mean A1C did not decrease, but fasting glucose declined by 10.3% in the cinnamon group compared to 3.4% in the placebo group ($P = 0.046$).

Another nonrandomized, nonblinded, placebo-controlled study evaluated 25 postmenopausal women with stable type 2 diabetes on oral medications.[38] Patients were given 1.5 g of cinnamon once a day or placebo for 6 weeks. There were no significant differences between groups in A1C or fasting glucose.

A 90-day prospective, double-blinded study evaluated 1 g of cinnamon or placebo in 72 adolescents with type 1 diabetes.[39] There was no change in A1C between the groups or difference in final A1C (8.8 vs. 8.7; $P = 0.88$). There was also no change in daily insulin dose.

There were no significant changes in a 3-month, double-blinded, placebo-controlled trial in 57 subjects with type 2 diabetes who received 1 g of cinnamon or placebo daily.[40] Specifically, blood glucose, A1C, fasting lipids, and insulin levels did not change.

The active ingredient in cinnamon was previously thought to be hydroxychalcone but is now thought to be related to procyanidin type-A polymers, which may increase insulin sensitivity.[7,35] Cinnamon has been evaluated in both type 1 and type 2 diabetes. A meta-analysis of five randomized, controlled trials in 282 people found that A1C does not decrease, although potential benefits in individual studies include decreases in fasting glucose and lipids.[41]

Side effects are rare and include irritation if used topically[35] or exacerbation of rosacea.[42] There are no known interactions, although additive hypoglycemia may occur with secretagogues.[7] Cinnamon contains a coumarin component and warrants caution if anticoagulants are used.[7,35] The 1 g amount used in studies is roughly equivalent to about a half teaspoonful a day,[35] which may be used in cereals, beverages, breads, and other foods. An aqueous cinnamon extract high in polyphenols may potentially improve metabolic syndrome and polycystic ovary syndrome.[43,44]

Fenugreek (*Trigonella foenum-graecum*)

Fenugreek is a member of the *Leguminosae* or *Fabaceae* family and grows well in India, Egypt, and other parts of the Middle East.[7] Fenugreek leaves are consumed as a vegetable in India.[7] It is used as a cooking spice and flavoring agent. In diabetes, the part used medicinally is the seed. Other medicinal uses include treatment of constipation, hyperlipidemia, and post-pregnancy to promote lactation,[7] although there are no studies supporting this use.

Most studies are short term and do not adequately report details. In one 10-day study, 10 patients with type 1 diabetes were assigned to placebo or twice-daily fenugreek (100 g/day) defatted seed powder in unleavened bread.[45] Fasting glucose decreased from an average baseline of 272 to 196 mg/dl ($P < 0.01$). Total cholesterol decreased ($P < 0.001$), as well as triglycerides and LDL cholesterol ($P < 0.01$ for both).

A 6-month trial evaluated 60 patients with inadequately controlled type 2 diabetes.[46] Twice-daily fenugreek seed powder (25 g/day) was given with meals. Mean fasting glucose

decreased from 151 to 112 mg/dl after 6 months. ($P < 0.001$) Postprandial glucose values and 1 and 2 hours after meals also declined significantly. Average A1C decreased from 9.6 to 8.4% after 8 weeks ($P < 0.001$).

In a different study, 25 newly diagnosed type 2 diabetic patients were given a hydroalcoholic fenugreek extract or placebo plus usual care of diet and exercise for 2 months.[47] The fenugreek group received 1 g/day of the seed extract. Results did not differ from the placebo group in fasting or postprandial glucose, although patients receiving fenugreek had improved area under the curve blood glucose and insulin levels ($P < 0.001$) and improved triglycerides and HDL cholesterol.

Fenugreek has been used for centuries, but few studies confirm its efficacy in diabetes control. Fenugreek contains saponins, glycosides, and other chemical constituents.[7] It may have beneficial effects in pancreatic and other tissues and may improve glucose and carbohydrate absorption, as well as decrease insulin resistance.[11,48,49]

Side effects are mostly uncomfortable gastrointestinal effects.[7] Although many women use fenugreek as a galactogogue, they should be informed that there are no studies that confirm this benefit and that fenugreek may appear in breast milk. Caution is warranted in those who have a peanut allergy or are allergic to the chickpea family because these are also members of the *Leguminosae* family, and fenugreek consumption may result in an allergic reaction.[50] Individuals who take antiplatelet agents, anti-inflammatory drugs, or herbs that have blood-thinning effects and pregnant women should not use fenugreek.[7,51]

The fenugreek dose used is variable, and a typical dose is 10–15 g/day as a single dose or divided with meals or 1 g of a hydroalcoholic extract. Patients who combine fenugreek with insulin or secretagogues may experience hypoglycemia.

Asian Ginseng (*Panax ginseng C.A. Meyer*) and American Ginseng (*Panax quinquefolius L*)

Ginseng is a botanical product that has been used medicinally for centuries. The root of two different forms are used for diabetes, Asian ginseng (*Panax ginseng C.A. Meyer*) and American ginseng (*Panax quinquefolius L*).[7,52] Both forms have been promoted as sports performance enhancers or "ergogenic aids," but studies do not support this use. Asian ginseng has been used for cancer prevention and for erectile dysfunction.[7]

In a randomized, double-blinded study of Asian ginseng in 36 newly diagnosed type 2 diabetic patients, 12 each were assigned to placebo, 100 mg/day, or 200 mg/day of Asian ginseng.[53] At the end of the 8-week study, fasting glucose declined (results significant only for the 100-mg group, $P < 0.05$). Mean A1C levels at the end were 6.5, 6.5, and 6%, respectively, for the three groups ($P < 0.05$ for the 200-mg group only).

In a different study, people with and without diabetes were given a 25-g oral glucose tolerance test (OGTT), with 3 g of American ginseng or placebo.[54] In people without diabetes, there was no difference in postprandial glucose when ginseng was taken right before the OGTT, but when it was taken 40 minutes before the OGTT, postprandial glucose decreased significantly. ($P < 0.05$ vs. placebo). In diabetic patients, postprandial glucose decreased regardless of ginseng administration time. The same researchers studied 3, 6, or 9 g of ginseng versus placebo. Blood glucose decreased in all ginseng groups compared to the control group, and no differences in glucose reduction were associated with the different doses.[55]

It is estimated that 6 million Americans use ginseng on a regular basis.[7] Although different species are available, Asian and American ginseng are used for diabetes. Ginsenosides are the active ingredients, and a variety of mechanisms may be responsible for their effect.[52,56–58]

Manufacturing problems have been reported; one analysis found that ginseng content varied from less (12%) to more (137%) than was indicated on the label.[59] The most common side effect is insomnia, although some people experience anxiety, headache, and increased blood pressure.[7,52] Many significant potential drug interactions may occur, so this is a product that should be used with caution when taking other medications.[7,52] For example, using ginseng may induce diuretic resistance and may also decrease the anticoagulant activity of warfarin.

The generally recommended dose of Asian ginseng is 200 mg daily.[7] The typical dose of American ginseng is 3 g before a meal.[7]

Gymnema (*Gymnema sylvestre*)

Gymnema sylvestre has been used in traditional Ayurvedic medicine. It is also known as "gurmar," meaning the "sugar destroyer" because it dulls the ability to taste "sweetness."[60,61] In India, gymnema has been traditionally used to treat diabetes.[60,61] Gymnema grows in tropical forests in India, and the leaves are used for medicinal purposes.[60,61]

Gymnema has been researched since the 1930s, mostly in India and other countries.[61] In one study, a dose of 200 mg twice a day for 6–30 months in 27 patients with type 1 diabetes resulted in an average A1C decline from 12.8 at baseline to 9.5% after 6–8 months ($P < 0.001$), and after 16–18 months, 22 individuals remaining on gymnema had a mean A1C of 9% (P not reported).[62] Average fasting glucose declined from 232 to 152 mg/dl after 20–24 months. Average insulin dose decreased from 60 to 45 units/day after 6–8 months and to 30 units/day after 26–30 months. P values were not reported for decreases in fasting glucose or insulin doses. In the control group of 37 patients on insulin, there was no change in blood glucose or A1C.

In a different study, 22 type 2 diabetic patients on sulfonylurea treatment took 400 mg daily for 18–20 months.[63] Average A1C declined from a baseline of 11.9 to 8.5% ($P < 0.001$), and average fasting glucose decreased from a baseline of 174 to 124 mg/dl after 18–20 months ($P < 0.001$). Five people discontinued sulfonylurea treatment. Lipids also significantly declined. The control group had no significant changes in A1C, glucose, or lipids.

Gymnema has been studied for up to 2 years in a small study in type 1 diabetic patients.[62] Gymnema contains gymnemosides and amino acids.[60,61] It exhibits a variety of effects that stimulate β-cell function as well as glucose uptake and utilization.[60,61,64–66] Residual β-cell function may be necessary because gymnema does not lower glucose in pancreatectomized animals.[67] Some authors have conjectured that gymnema may help treat obesity because gymnemic acid binds to taste buds where sugar binds and thus may prevent sugar craving.[60]

If used, a standardized extract should be chosen. This product has not been studied in pregnant or lactating women or in children or the

elderly and therefore should not be used. The main potential adverse effect is hypoglycemia. Gymnema extract is being studied in the United States in combination with other diabetes medications. A typical dose is 400 mg/day, standardized to contain 24% gymnemic acids.

Milk Thistle (*Silybum marianum*)

Milk thistle is a member of the aster family (*Asteraceae or Compositae*), which also includes thistles and daisies.[7,68] Milk thistle contains silymarin, consisting of silybin, silychristine, and silidianin.[7,68] These medicinal components are found in the fruit, seeds, and leaves of the plant.[7,68] Milk thistle has been evaluated in patients with type 2 diabetes and to treat hepatic diseases, protect against hepatotoxic agents, and for nonalcoholic steatohepatitis.[7,69,70]

Milk thistle was evaluated in a randomized, open-label trial in 60 patients on insulin with type 2 diabetes and cirrhosis.[69] Half received 600 mg/day of silymarin, and the other half received a placebo for 12 months. Mean fasting glucose declined in the milk thistle group from 190 mg/dl at baseline to 165 mg/dl at 12 months ($P < 0.01$ vs. baseline). A1C decreased from 7.9% at baseline to 7.2% at end point ($P < 0.01$ vs. baseline). Mean daily insulin dose decreased from 55 to 42 units/day at end point ($P < 0.01$ vs. baseline).

In another double-blinded study, 25 patients with type 2 diabetes on oral agents were randomized to 300 mg twice daily of silymarin seed extract, and 26 to placebo for 4 months.[71] A1C decreased significantly in the silymarin group (from 7.8 to 6.8% after 4 months, $P < 0.001$) and significantly increased in the placebo group (from 8.3 to 9.5%, $P < 0.0001$). Fasting blood glucose declined significantly from 156 to 133 mg/dl in the silymarin group ($P < 0.001$) and increased significantly in the placebo group (from 167 to 188 mg/dl, $P < 0.0001$). LDL cholesterol and triglycerides also decreased significantly in the silymarin group.

A 4-month multicenter, randomized, double-blinded, placebo-controlled trial in 59 people with type 2 diabetes evaluated the use of milk thistle.[72] One group received silymarin 200 mg plus glyburide 10 mg daily, another group received glyburide plus placebo, and a third group received glyburide only. A1C decreased significantly ($P < 0.05$) in the milk thistle plus glyburide group, from 8.9 to 7.45%. Fasting glucose also declined significantly from 211 to 167 mg/dl. In the glyburide-plus-placebo group, A1C decreased from 8.76 to 8.71% (not statistically significant) and fasting glucose declined significantly from 202 to 193 mg/dl ($P < 0.05$). In the glyburide-only group, A1C decreased from 8.78 to 8.74% (not statistically significant) and fasting glucose increased significantly from 193 to 199 mg/dl ($P < 0.05$). The authors stated that the silymarin group had significantly greater improvement in A1C and fasting glucose than the other two groups. Finally, area under the curve decreased 36.8% from baseline in the silymarin-plus-glyburide group, but was unchanged in the other two groups.

Milk thistle is thought to be an insulin sensitizer.[68,69,72] Adverse effects may include gastrointestinal upset and cross-allergic reactions with members of the daisy and marigold family, including ragweed and chrysanthemums.[7,68] Milk thistle may have estrogenic effects, and thus women with breast or uterine cancer should avoid its use. Interestingly, milk thistle may inhibit beta glucuronidase and thus increase clearance of administered estrogens.[7] It may inhibit certain isoenzymes in the cytochrome P450 system, such as CYP 2C9, and subsequently increase serum concentrations of warfarin. It may also affect glucuronidation and thus affect serum concentrations of certain statins, anticonvulsants, and benzodiazepines.[7]

The dose of milk thistle for liver disease and in the diabetes studies discussed is 200 mg three times daily. Milk thistle extract should be standardized to contain 70% silymarin (140 mg silymarin).[68] Preparations that contain phosphatidylcholine may be dosed at 100 mg/day because phosphatidylcholine enhances oral absorption.[68]

Nopal (*Opuntia streptacantha*)

Nopal, or prickly pear, is a member of the cactus family. Multiple species are known as *Opuntia*, including *Opuntia ficus indica, Opuntia megacantha,* and *Opuntia streptacantha*.[7] Nopal is used as a food by Hispanic individuals, and the leaves, flowers, stems, or fruit are the parts used. Nopal may also be added to other ingredients in a fruit smoothie. Broiled stems or nopal extracts are used to lower blood glucose and to treat hyperlipidemia[7] and benign prostatic hyperplasia[73] and to reduce alcohol hangover symptoms.[74]

Trials studying nopal have included only a few patients for short periods of time and have mostly been published in Spanish, although abstracts are available in English. They have shown decreases in glucose.[75,76] One study in 36 patients revealed that, when added to traditional Mexican breakfasts, nopal significantly decreased incremental area under the blood glucose response curves ($P = 0.013$, 0.011, and 0.019 when added to "chilaquiles, burritos, and quesadillas," respectively).[77]

Nopal may help lower blood glucose when cooked or taken as a dietary supplement, although some individuals may prepare a blended shake using raw nopal. Nopal contains fiber and pectin, which may decrease carbohydrate absorption and enhance insulin sensitivity.[7,78] Nopal exhibits hypoglycemic activity in pancreatectomized animals.[79]

Diarrhea and increased stool volume are common side effects.[7] When nopal is combined with sulfonylureas, there is additive improvement in blood glucose.[80] Nopal has been highly consumed as a food, but it has not been studied adequately as a dietary supplement. The dose is 100–500 g daily of broiled stems. Optimal doses of extracts have not been established to treat diabetes.

Salacia (*Salacia oblonga; Salacia reticulata*)

Salacia is a woody climber plant native to India and Sri Lanka that is used as a traditional Ayurvedic medicine. The roots and stems are used for glycemic control and weight loss.[7,81] It has been extensively marketed in Japan as both a food and nutritional supplement, and its use is emerging in the United States for type 2 diabetes.[7,82,83] It has also been prepared as a tea.[83]

Few studies have evaluated salacia in type 2 diabetes. One was a randomized, double-blinded crossover trial in 51 people with type 2 diabetes treated with oral agents.[83] Patients were randomized to Kothala Himbutu tea containing *Salacia reticulata* and other plant products or a placebo for 3 months and then crossed over to the other group for an additional 3 months. A1C at endpoint was lower in the salacia group (6.29% for salacia vs. 6.65% for placebo, $P = 0.008$).

Another three-period, three-treatment randomized, double-blinded study was performed in 66 people with type 2 diabetes on oral agents.[84] Subjects were randomized to one of three treatments: a liquid meal replacement, a meal replacement plus 240 mg of *Salacia oblonga*, or a control meal plus 480 mg of salacia. The adjusted peak values 180 minutes after ingestion were significantly lower in the salacia groups compared to the control group: 160 mg/dl in the control group, 130 mg/dl in the 240-mg salacia group (19% reduction), and 116 mg/dl in the 480-mg group (27% reduction; $P < 0.0001$ for both doses versus control).

Active ingredients of salacia include salacinol, kotalanol, kotalagenin-16 acetate, and mangiferin.[81] The active ingredients have a variety of actions including postprandial glucose decrease by inhibiting α-glucosidases in the intestinal brush border and thus slowing carbohydrate breakdown into absorbable monosaccharides. The mechanism of action is therefore similar to prescription α-glucosidase inhibitors such as acarbose. Other pharmacological activity includes modulation of lipogenic gene transcription through peroxisome proliferator–activated receptor-α activity and modalities that may help reduce diabetes-related complications, such as aldose reductase inhibition and renin-angiotensin system modulation. Catechin and tannin content may contribute to weight loss properties.[7,85] Side effects noted in a study in healthy volunteers included dose-related gastrointestinal upset such as flatulence and distension,[7,82] and there may be potential additive hypoglycemia if used in combination with secretagogues or insulin.[7] It has been used as a tea before meals as well as in doses of 240 or 480 mg in combination with a meal in type 2 diabetic patients or up to 1,000 mg in healthy volunteers.[7,82–84] Lowering of A1C has been shown, as well as a dose-related decline in postprandial glucose.

Salvia hispanica L, or "Chia"

Another popular supplement, is *Salvia hispanica*, also known as "chia," which means "oily." This plant grows to be about 1 meter in height and has purple or white flowers that grow in clusters on a stem. The plant is grown in Latin America, and the seed is primarily used in supplements and added to foods.[7,86] The famous "chia pets" are sprouts of this plant grown on clay figures. A plant source of omega-3 fatty acid, alpha linolenic acid, salvia also contains fiber, protein, calcium, magnesium, iron, and antioxidants.[86]

A single-blinded crossover study evaluated A1C, blood glucose, blood pressure, and other cardiovascular risk factors in 20 people with type 2 diabetes.[86] Subjects were randomized to a daily dose of 37 g of salvia or wheat bran (control group) for 12 weeks and then crossed over to the other group after a washout of 4–6 weeks. A1C declined significantly from baseline in the salvia group (from 6.9 to 6.7%, $P < 0.05$) but did not change in the control group (6.9% at baseline and 12 weeks). Systolic and diastolic blood pressure declined in the salvia group (from 129 to 123 mmHg [$P < 0.05$] and from 81 to 78 mmHg [P not significant], respectively) and increased in the control group (from 122 to 129 mmHg and from 76 to 79 mmHg, respectively [$P < 0.05$ for both]). Other cardiovascular risk factors declined in the salvia group but increased in the control group.

Salvia is rich in plant omega-3 fatty acids, which may benefit people with diabetes. The potential therapeutic benefit is decreased postprandial glucose and insulinemia, which may be the result of the viscosity of the soluble fiber it contains.[86]

At this point, there are no known side effects or drug interactions, but preliminary information indicates that salvia may increase triglycerides in people with baseline hypertriglyceridemia.[87] It may also increase the risk of prostate cancer.[88]

Clinical laboratory parameters, including lipids levels, renal function, and coagulation factors, have been evaluated, and no abnormalities occurred.[86] There are no known drug interactions.

Although salvia is found in supplement form and dosed at 37 g/day, the seed may be sprinkled on yogurt, soup, or salad.[86] Evidence for its use is emerging, and although blood glucose, blood pressure, and markers of cardiovascular disease may benefit, patients using it should have their triglycerides monitored, and males at risk for prostate cancer should avoid its use.

Conclusions

Evidence for dietary supplements use in people with diabetes is emerging but is still controversial because of the paucity of rigorous clinical trials. It is important for clinicians to remember to be respectful of their patients who wish to use these products. Providing unbiased information and education about dietary supplements is important to optimizing patient care. Because dietary supplements are pharmacologically active, it is important for health care providers to understand their chemical constituents, theorized mechanisms of action, side effects, and potential drug interactions.

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