

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

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 patients²² 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 μ g/day for 64 months have not resulted in adverse effects,³⁰ a typical dose is 200 μ g/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 μ g/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 Administration 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, non-blinded, 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, fast-

ing 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 topically³⁵ 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

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, anti-convulsants, 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 glu-

case and to treat hyperlipidemia⁷ and benign prostatic hyperplasia⁷³ 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.^{77,78} 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, $P = 0.008$).

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