In Brief

Several botanical and biological products claim to lower blood glucose or decrease complications of diabetes, and some of these are being used by people with diabetes. Products thought to lower blood glucose include gymnema, fenugreek, bitter melon, ginseng, and nopal. Claims have also been made for aloe, bilberry, and milk thistle, but there is less evidence in support of these. Botanical products thought to decrease diabetes complications include γ-linolenic acid, ginkgo biloba, and garlic. A vitamin-like substance, α-lipoic acid, has been used to treat neuropathic complications.

Biological Complementary Therapies: A Focus on Botanical Products in Diabetes

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No one has thoroughly determined how many patients with diabetes use complementary therapies. A recent survey of diabetes educators in the western half of the United States[1] evaluated the most frequently recommended and used alternative therapies. These included physical activity, self-help groups, lifestyle diets, laughter and humor, relaxation therapy, prayer, imagery/visualization, meditation, massage, and music therapy. Although botanical products were included in the survey, they were not frequently recommended or used.

Another survey of alternative treatments used by patients with diabetes[2] did indicate that herbal treatments are used along with other modalities. In some cases, patients used these treatments instead of conventional medications, and severe complications, including increased hospitalizations, ketoacidosis, and acute hyperglycemia, occurred.

Technically, an herbal product is made from the leaves and roots of a plant, whereas a botanical product includes parts or pieces from the whole plant. However, these terms are often used interchangeably in discussions of complementary therapies.

CONCERNS ABOUT BIOLOGICAL OR BOTANICAL THERAPIES

As with conventional medicines, the use of complementary therapies raises concerns about possible side effects[3] and drug interactions.[4] Patients using complementary therapies have experienced many serious side effects; in some cases, they may attribute these effects to another medication. Because patients often take medications to treat their diabetes, concomitant use of complementary therapies may also result in toxicity secondary to exaggerated effects or sub-therapeutic effects of their conventional medications.

Another concern relates to the variability of products. Botanical products are available in capsules and tablets, as well as in other forms, such as water extracts (also called decoctions or infusions), tinctures (hydroalcoholic extracts), and glycerites (glycerin-extracted preparations that are alcohol-free). All vary in potency. In addition, product quality may depend on what part of the plant was used, how it was stored, how long it was stored, the processing technique, and how the extract was prepared.[3]

Some products are available in a form standardized for pharmacological activity. This should guarantee that there is consistency from batch to batch and that the active ingredients are stable.[5] However, standardization is not simple because, for many botanicals, the active constituents are unknown. A product may be standardized for one or more biologically active compounds, but that com-

pound may not be the active ingredient. Pharmacological action may come from the additive or synergistic effects of several ingredients, none of which separately has the same activity as the whole plant.[6] Furthermore, active constituents in extracts or dried botanicals may vary secondary to geographical or soil differences, differences in exposure to sunlight or rainfall, differences in the time of harvest, and differences in the methods of drying, storing, and processing. All of these variables may affect pharmacological activity.[7]

Other factors involve potential misidentification, mislabeling, and possible addition of unnatural toxic substances, such as adulteration with heavy metals or steroids and contamination with microbes, pesticides, fumigants, and radioactive products.[7]

BOTANICAL PRODUCTS THAT MAY LOWER BLOOD GLUCOSE LEVELS

Gymnema

A member of the milkweed family, gymnema (Gymnema sylvestra) is a woody plant found in tropical forests of India and Africa.[8–10] For more than 2,000 years, people have chewed its leaves to treat "madhu meha" ("honey urine").[9] Used in Ayurvedic medicine, it is thought to destroy a person's ability to discriminate sweet taste; hence, it is often called "gurmar" or "sugar destroyer."[8]

Chemical constituents of the plant include the gymnemic acids (gymnemosides), saponins, stigmasterol, quercitol, and the amino acid derivatives betaine, choline, and trimethylamine.[8] Gymnema has been used for centuries to treat diabetes.[10]

Proposed mechanism of action. Although the exact mechanism is unknown, there are a variety of theorized mechanisms. Besides impairing the ability to discriminate sweet taste, gymnema increases the enzyme activity responsible for glucose uptake and utilization.[11] It may stimulate β-cell function, increase β-cell number, and/or increase insulin release by increasing cell permeability to insulin.[8,12] In pancreatectomized animals, it has no hypoglycemic effect, indicating that its effect may require some residual β-cell function.[13]

Side effects and drug interactions. No side effects have been reported secondary to gymnema use. Hypoglycemia is a potential side effect;[10] drug interactions may occur from the additive effects when used concomitantly with hypoglycemic agents.

Clinical studies. There are only a few human studies, and these do not report important design details, such as blinding or randomization.

One study[14] was conducted in type 1 diabetic patients on insulin, 27 of whom took 200-mg gymnema capsules after breakfast and supper and 37 of whom took insulin only for a period of 6–30 months. After 6–8 months, mean HbA_{1c} decreased in the gymnema group from a baseline of 12.8 to 9.5% ($P < 0.001$). After 16–18 months, 22 patients remaining on gymnema had a mean HbA_{1c} of 9% (*P* values not given). At the end of 26–30 months, six patients remaining on gymnema had a mean HbA_{1c} of 8.2% (*P* values not given).

Mean fasting blood glucose (FBG) also decreased from a baseline of 232 to 177 mg/dl after 6–8 months 150 mg/dl after 16–18 months, and 152 mg/dl after 20–24 months (*P* values not given). The mean insulin dose decreased from a baseline of 60 to 45 units/day after 6–8 months and to 30 units/day at 26–30 months (*P* values not given). Patients on placebo had no significant changes from baseline.

Another study[15] was conducted in patients with type 2 diabetes on sulfonylureas; 22 took 400 mg/day of gymnema capsules in addition to sulfonylurea treatment, and 25 took a placebo and sulfonylureas for a period of 18–20 months. Mean HbA_{1c} decreased from a baseline of 11.9 to 8.48% ($P < 0.001$). Mean FBG decreased from 174 to 124 mg/dl after 18–20 months ($P < 0.001$). Five patients were able to discontinue sulfonylureas. In this study, lipids also decreased significantly. Patients on placebo had no significant changes in HbA_{1c}, FBG, or lipids.

Clinical notes. Because of the possibility of hypoglycemia when gymnema is used with insulin or other diabetes agents, doses for existing diabetes therapies may have to be adjusted with the addition of gymnema. This product should not be used without medical supervision. A typical dose is 400 mg/day standardized to contain 24% gymnemic acids.[8,10]

Fenugreek

Fenugreek (Trigonella foenum-graecum) has been used as a cooking spice and flavoring agent for centuries.[9] It is a member of the Leguminosae family, along with other legumes.[9,10] The plant grows in India, Egypt, and the Middle East.[9]

Fenugreek has also been used as a medicinal agent to treat diabetes, constipation, and hyperlipidemia.[10] It has been used topically to treat inflammation, and it has been used postpartum with a substance called jaggery to promote lactation. Because its taste and odor resemble maple syrup, it has been used to mask the taste of medicines.[9]

Chemical constituents of the plant include saponins, many of which are glycosides of diosgenin.[9] The seeds also contain the alkaloids trigonelline, gentianine, and carpaine compounds. Other components of the seeds include several C-glycosides. The seeds contain up to 50% mucilaginous fiber.[9] Other seed constituents include 4-hydroxyisoleucine, an amino acid, and fenugreekine.

Proposed mechanism of action. Fenugreek is thought to delay gastric emptying, slow carbohydrate absorption, and inhibit glucose transport.[16] It has been shown to increase erythrocyte insulin receptors and improve peripheral glucose utilization, thus showing potential pancreatic as well as extrapancreatic effects.[17]

Various components of the seeds have varying activities. For example, the component called fenugreekine, a steroidal sapogenin peptide ester, may have hypoglycemic properties.[10] Trigonelline, another component, may exert hypoglycemic effects in healthy patients without diabetes,[10] but other studies have shown that fenugreek has no effect on fasting or postprandial blood glucose levels in nondiabetic subjects.[18]

Side effects and drug interactions. The main side effects are flatulence and diarrhea, which subside after a few days. However, fenugreek also has uterotonic properties.[10] Hypersensitivity reactions have also been reported,[10] including rhinorrhea, wheezing, and fainting after inhalation of the fenugreek-seed powder. Wheezing and facial angioedema after application of a topical fenugreek paste for dandruff was reported in a patient with chronic asthma.[19]

Because fenugreek is a member of the Leguminosae family, which includes peanuts,[9] it is theoretically possible for someone with a peanut allergy to react to fenugreek. However, this reaction has never been reported.

All of fenugreek's side effects may

occur in infants of nursing mothers who use this substance.

Because of the coumarin constituents, fenugreek may potentially enhance anticoagulant activity of drugs or herbs that have antiplatelet activity.[10] It may inhibit corticosteroid drug activity, interfere with hormone therapy, and potentiate monoamine oxidase (MAO) inhibitor activity. A theoretical interaction is decreased or delayed absorption of concomitant medications because of the high mucilage content. Additionally, there may be additive hypoglycemic activity when combined with diabetes medications.[10]

Clinical studies. There are few human studies, and most of these are short-term, involve few patients, and do not adequately report study design details.

In one study,[20] 10 patients with type 1 diabetes on insulin underwent a 10-day metabolic trial. Patients were blinded, but it was unclear whether the investigators were blinded. Patients were randomized to either placebo or 50 g fenugreek defatted seed powder twice a day in chapati (unleavened bread). Mean FBG decreased from a baseline of 272 to 196 mg/dl ($P < 0.01$). Patients also demonstrated a statistically significant decline in serum total cholesterol ($P < 0.001$), triglycerides, and LDL cholesterol ($P < 0.01$ vs. placebo for triglycerides and LDL), but no change in HDL cholesterol.

The largest fenugreek study[21] was a 6-month trial in 60 patients with inadequately controlled type 2 diabetes. The authors did not provide information on randomization or blinding. Patients were administered a 75-g oral glucose tolerance test (OGTT) to determine mean baseline parameters. Fenugreek seed powder, 25 g/day, was administered in two equal doses with lunch and dinner for 6 months. Mean FBG decreased from a baseline of 151 to 112 mg/dl after 24 weeks. The mean 1-h OGTT baseline was 284 mg/dl, compared to 196 mg/dl after 24 weeks. Mean 2-h values decreased from a baseline of 257 to 171 mg/dl after 24 weeks ($P < 0.001$ vs. baseline for both). Mean HbA_{1c} decreased from a baseline of 9.6 to 8.4% after 8 weeks ($P < 0.001$). Although 40 patients were on oral diabetes medications, the authors did not report on whether they were able to decrease their doses or discontinue their diabetes drugs.

Clinical notes. Fenugreek has been categorized as "generally recognized as safe" in the United States.[10] Dose recommendations vary depending on the source. However, all recommended doses are much lower than those used in the clinical studies, which ranged from 15 g mixed in water to 50 g twice daily. One source recommended 1–2 g of the seed or its equivalent three times daily or 1 cup of the tea, made by steeping 500 mg seed in 150 ml cold water several times a day.[10]

Bitter Melon

Bitter melon (Momordica charantia), also known as bitter gourd, bitter apple, bitter cucumber, karolla, and karela, is a vegetable cultivated in tropical areas, including India, Asia, South America, and Africa. It is yellow-orange with a bumpy exterior resembling a gherkin and is bitter but edible.[9]

Bitter melon has been used to treat diabetes and psoriasis and for HIV supportive therapy, and it has been studied as a potential contraceptive agent.[9,10] It has been taken for centuries as a dietary treatment and more recently has been used as an injectable extract for research.[22]

Bitter melon contains several chemical constituents, including the glycosides mormordin and charantin. Charantin contains mixed steroids with hypoglycemic activity. Another component is the peptide polypeptide-P.[9] Bitter melon also contains the alkaloid mormordicine. Its seeds contain the abortifacients α-mormorcharin and β-mormorcharin, as well as the pyrimidine nucleoside vicine.[9]

Proposed mechanism of action. The fruit and seeds of bitter melon are thought to exert hypoglycemic effects in normal and diabetic animal models.[10] The specific components thought to contribute to its hypoglycemic activity include charantin, polypeptide P, and vicine. Other theoretical actions include extrapancreatic activity, such as increased tissue glucose uptake, liver/muscle glycogen synthesis, and decreased blood glucose synthesis through depression of the enzymes glucose-6-phosphatase, fructose-1, and 6 bisphosphatase, and enhanced glucose oxidation by enzyme G6PDH pathway.[9]

Side effects and drug interactions. Bitter melon may produce digestive tract discomfort.[9] Hypoglycemic coma from a tea containing bitter melon[10] has been reported. Favism (acute hemolytic anemia characterized by headache, fever, abdominal pain, and coma) has also been reported from one of the seed constituents of bitter melon, vicine.[10] The red arils around bitter melon seeds have produced toxicity; in one child, vomiting, diarrhea, and death occurred.[9] Bitter melon has abortifacient effects[9,10] and in animals has produced hepatotoxicity.[10]

Concomitant use with stimulant laxatives or other agents that decrease potassium may increase the risk of potassium depletion.[10] If combined with secretagogues, additive hypoglycemia may occur. This was reported when a patient used both bitter melon and chlorpropamide.[23]

Clinical studies. Most studies in humans involve very small numbers, are of very short duration, and have been reported with only sketchy information about details of study design, including blinding and randomization. Although there are several studies using bitter melon, only studies in which glucose values were reported will be discussed.

An early study of 19 patients (11 with type 1 and 8 with type 2 diabetes)[22] used polypeptide-P zinc chloride, a momordica extract, prepared in the same manner as bovine insulin. This "plant insulin" was injected subcutaneously in five patients with type 1 diabetes and six patients with type 2 diabetes. No details of randomization or blinding were provided. FBG was measured at the time of injection, as well as 4, 6, 8, and 12 h after injection. The control group, consisting of six patients with type 1 and two patients with type 2 diabetes, did not receive any treatment.

In the patients with type 1 diabetes, mean FBG decreased from 304 to 169 mg/dl 4 h after injection ($P < 0.05$), and this effect was maintained at 6 and 8 h after injection (FBG 176 and 174 mg/dl, respectively, $P < 0.05$ compared to baseline). At 12 h, FBG had started to increase (208 mg/dl).

In the patients with type 2 diabetes, changes were significantly different between the experimental and control groups at 1 and 6 h ($P < 0.05$). However, there were no significant differences from baseline in the experimental group. In the control groups of both the type 1 and type 2 diabetes interventions, blood glucose values were not significantly changed from baseline.

The largest study using bitter melon[24] was done in 100 type 2 diabetic patients but was conducted for only 2 days using an aqueous suspension of the vegetable pulp. Day 1 mean FBG was 152 mg/dl, and after a 75-g OGTT, the mean 2-h postprandial glucose level was 257 mg/dl. On day 2, momordica extract was given, and blood glucose was measured 1 h later. This mean value was 131 mg/dl and was significantly different from the FBG of 160 mg/dl ($P < 0.001$). Patients then received a 75-g oral glucose load, and blood glucose was sampled 2 h later. The mean 2-h blood glucose was 222 mg/dl. One hour after momordica was given, 86 patients had decreased values and an attenuated blood glucose response to the 75-g glucose load, in comparison to the previous day (222 vs. 257 mg/dl, *P* value not significant).

Clinical notes. There is insufficient information to recommend a reliable dose.[10] Various forms of bitter melon have been used in research, including powder, extract, juice, as well as the cooked vegetable. Some sources have stated that 50 ml fresh juice taken daily with food may be used.[10] Tinctures are becoming available. Medical supervision is always necessary when using bitter melon.

Ginseng

A variety of products are called "ginseng." The most commonly used are three different botanicals: Asian or Korean ginseng (Panax ginseng C.A. Meyer), American ginseng (Panax quinquefolius L.), or Russian or Siberian ginseng (Eleutherococcus senticosus Maximum). The part used is the root.[25]

Ginseng has been described as an "adaptogen"—a drug that may increase resistance to adverse influences such as infection and stress.[25] Individuals use ginseng in an attempt to enhance physical performance, psychomotor performance, and cognitive function; for immunomodulation; and as treatment for infections and diabetes.[26] Generally, length of use is up to 3 months, with possible repeated courses.[27] In diabetes, only Korean and American ginseng have been studied, so this discussion will be limited to these two substances.

Ginseng contains a family of steroid-like compounds called ginsenosides. Although there are many subtypes, ginsenosides are tetracyclic triterpenoid saponin glycosides thought to have various hormonal and central nervous system (CNS) effects. Some ginseng compounds show contradictory effects; for example, ginsenoside Rg1 has hypertensive and CNS-stimulant effects, whereas ginsenoside Rb1 has hypotensive and CNS-depressant effects.[9,25]

Proposed mechanism of action. In diabetes, the mechanism of beneficial effect is unknown. Animal research has indicated that ginseng may lower blood glucose by possibly decreasing the rate of carbohydrate absorption into the portal hepatic circulation[28] and possibly increasing glucose transport and uptake.[29] Another potential mechanism is modulation of insulin secretion.[30] Some ginseng fractions have increased serum insulin levels and glucose-stimulated insulin secretion in mice.

Side effects and drug interactions. The most commonly reported side effects include nervousness and excitation.[9] Other effects include headache, hypertension, insomnia,[9,10] estrogenic effects including mastalgia,[31] vaginal bleeding,[32] and cerebral arteritis.[33]

"Ginseng abuse syndrome" is a controversial adverse effect that was reported in 14 of 133 long-term users of high daily doses.[34] This syndrome consisted of hypertension, nervousness, sleeplessness, skin eruptions, increased libido, and morning diarrhea.

Several drug interactions have been reported. Diuretic resistance can occur when ginseng is used in conjunction with a diuretic.[35] Tremors[36] and hypomania[37] can occur when it is given with phenelzine, an MAO inhibitor. Insomnia, headache, and decreased warfarin effect have also been reported.[38] Concomitant use with diabetes agents may cause hypoglycemia. If combined with stimulants, ginseng may potentiate stimulant effects.[10]

Clinical studies. Ginseng has been evaluated in many studies of varying quality. A recent meta-analysis that evaluated its effects on physical or psychomotor performance, cognitive function, immunomodulation, and other outcomes[26] drawing on only randomized, placebo-controlled studies showed that ginseng has suboptimal efficacy.

Ginseng has only been studied in type 2 diabetes. In a randomized, double-blind study of ginseng in 36 newly diagnosed type 2 diabetic patients,[39] 12 people each were assigned to placebo, 100 mg/day, or 200 mg/day of ginseng tablets for 8 weeks. At the end of the study, mean FBG values for the three groups were 149, 139, and 133 mg/dl, respectively. (Results were only statistically significant for the 100-mg/day group, $P < 0.05$.) Baseline values were not reported, and average HbA_{1c} levels at the end of the study were 6.5, 6.5, and 6.0%, respectively ($P < 0.05$ for 200-mg group).

Another study compared the effects of American ginseng and placebo in patients with and without type 2 diabetes.[40] Ten patients without diabetes and nine patients with type 2 diabetes were given a 25-g OGTT, with and without 3 g of ginseng capsules. Patients were given ginseng 40 min before or with the glucose challenge. Patients were blinded, but the authors did not state whether the investigators were blinded.

No significant difference in postprandial glucose was reported when ginseng was taken with the glucose challenge in patients without diabetes. Taking ginseng 40 min before the OGTT resulted in a significant reduction in postprandial glucose ($P < 0.05$ vs. placebo). In patients with diabetes, ginseng given either concomitantly or 40 min before the OGTT significantly lowered postprandial glucose ($P < 0.05$ vs. placebo).

Clinical notes. Ginseng products have been found to be adulterated with other substances including mandrake root or phenylbutazone,[9] and in one case even led to positive results on a "doping" test for an athlete.[41]

Typical doses are 200–600 mg/day.[10] These doses are lower than in the study using American ginseng capsules but a bit higher than the tablets used in the study of newly diagnosed type 2 diabetic patients. Besides capsules and tablets, ginseng comes in a variety of forms ranging from fresh and dried roots to extracts, solutions, sodas, teas, and cosmetics.[9] The root contains at least 1.5% ginsenosides.[27]

Some people use ginseng on a continual basis, but others use ginseng for a period of 3 weeks to 3 months.[10,27] Evidence for efficacy of ginseng is limited, at best.

Nopal

Nopal (Opuntia streptacantha Lemaire), also known as prickly pear, is a member of the cactus family.[9] Multiple species are known as Opuntia, including Opuntia megacantha, Opuntia ficus indica, and Opuntia fuliginosa. Research has focused on

Opuntia streptacantha Lemaire to lower blood glucose.

Nopal stems are used as a food source in Mexico.[10] The leaves contain mucopolysaccharide soluble fibers and phytochemicals. Leaves and stems are also used for other reasons, such as for diabetes control and treatment of hyperlipidemia.[10]

Proposed mechanism of action. Studies in pancreatectomized animals have shown that the hypoglycemic activity does not depend on the presence of insulin.[42] However, the mechanism of action is unknown. The fiber and pectin components are thought to have hypoglycemic activity. Because insulin concentrations decrease with nopal administration, enhanced insulin sensitivity is another theorized mechanism of action.[43]

Nopal's hypoglycemic activity has been reported to reach maximum effects 3–4 h posptrandially and to last up to 6 h.[10] The fiber content may affect intestinal uptake of glucose. Animal research indicates that the pectin component may alter hepatic cholesterol metabolism.[10]

Side effects and drug interactions. Reported adverse effects include increased stool volume and frequency and abdominal fullness.[44] Dermatitis has also been reported.[10] In a case report of 8-week coadministration with chlorpropamide, additive effects on blood glucose and insulin levels were found.[43] Additive hypoglycemia with secretagogues is a theoretical concern, although there have been no reports of this.

Clinical studies. Most trials are small and have been published in Spanish, although English abstracts are available. Two small trials have been published in English.

One trial involved three groups of patients with type 2 diabetes treated with diet alone or in combination with sulfonylureas.[45] Details of blinding or randomization were not provided. After a 12-h fast, 16 patients received 500 g broiled nopal (Group 1); 10 people received 400 ml water (Group 2); and 6 people received 500 g broiled zucchini (Group 3).

In Group 1, mean blood glucose declined from 222 mg/dl fasting to 203, 198, and 183 mg/dl after 60, 120, and 180 min, respectively ($P < 0.001$ compared to baseline). There was no significant drop in glucose in Group 2. In Group 3, broiled zucchini caused a drop from a mean baseline of 246 mg/dl fasting to 226, 219, and 206 mg/dl at 60, 120, and 180 min, respectively ($P < 0.05$ vs. baseline for 60 and 120 min; $P < 0.01$ vs. baseline at 180 min).

Another trial compared 14 patients with type 2 diabetes on sulfonylureas (Group 1) to individuals without diabetes (Group 2).[46] Details of blinding or randomization were not provided. Both groups received 500 g broiled nopal or 400 ml water.

In patients with diabetes, mean decreases in glucose concentrations were 21, 28, and 41 mg/dl at 60, 120, and 180 min, respectively, after nopal administration ($P < 0.005$ for 60 and 120 min vs. baseline; $P < 0.001$ for 180 min vs. baseline). There were no significant differences after water administration. Insulin concentrations also declined significantly with nopal. In patients without diabetes, there were no significant differences.

Clinical notes. Nopal is given with meals in doses of 500 g broiled or fresh nopal stems.[10] However, ideal doses and optimal preparation methods have not been established. There are no known risks with nopal use, but there have been no well-designed or long-term studies. Evidence in favor of nopal is limited at this time.

Aloe

Aloe is a desert plant with a cactus-like appearance. It belongs to the family Liliaceae.[9] There are more than 500 species, but the most familiar form is aloe vera. It has been used since prehistoric times for burns and wound healing.

There are two forms of aloe vera: dried juice from the leaf and aloe gel. Latex from pericyclic cells obtained beneath the skin of leaves may be evaporated to form a sticky substance known as "drug aloes" or "aloe." This aloe juice contains the cathartic anthraquinone, barbaloin, a glucoside of aloe-emodin, as well as other substances.[9]

Aloe gel is obtained from the inner portion of the leaves. It does not contain anthraquinones but does contain a polysaccharide, glucomannan, that is similar to guar gum.[9] Aloe gel is used topically, but it has also been used orally for diabetes.

Proposed mechanism of action. Aloe gel taken internally may produce a mild reduction in mean glucose levels, but the mechanism has not been elucidated.

Side effects and drug interactions. The laxative form of aloe may cause abdominal cramps, pain, and severe diarrhea, with subsequent fluid and electrolyte disturbances. This form may deplete potassium, predisposing people who use it to cardiac abnormalities. It may also potentially interact with glycosides because of the hypokalemic effects.[10] Additive hypokalemia may also occur when it is coadministered with other drugs that deplete potassium, such as diuretics or corticosteroids.[10] Additive cathartic effects may occur when combined with other laxatives. Topical use has not been reported to produce any problems.

Aloe gel taken internally may exacerbate Crohn's disease and ulcerative colitis. It may also produce additive hypoglycemia when taken concomitantly with secretagogues.[10]

Clinical studies. A very small, uncontrolled study was conducted in patients with type 2 diabetes.[47] Five patients were administered one-half teaspoonful, twice daily, of dried aloe sap for 4–14 weeks. Details were very sketchy, and information regarding blinding was not provided. FBG fell from a mean of 273 to 151 mg/dl ($P < 0.001$). Mean HbA_{1c} decreased from 10.6 to 8.2% (significance not reported).

Clinical notes. Aloe has been used topically and as a cathartic. It has also been used orally to boost the immune system and for treatment of asthma, ulcers, and diabetes.

Doses are variable and include 50–200 mg/day of aloe leaf gel.[10] There is insufficient evidence for the use of aloe in diabetes. Supplementation is not recommended.

Bilberry

Bilberry is a plant closely related to the American blueberry, cranberry, and huckleberry.[10] Two forms of bilberry are used: the dried fruit and the leaf. The dried fruit is used to treat diarrhea[27] and to improve visual acuity and night vision.[10,48] The leaf is used for diabetes, arthritis, circulatory disorders,[9,27] cataracts,[49] and varicose veins.[10] In folk medicine, it is used as a "blood sugar–reducing" drug, and is therefore a common constituent in "antidiabetic" teas.[50]

Proposed mechanism of action. Anthocyanosides are bioflavonoids, chemical constituents in bilberry fruit thought to be responsible for some of its vascular effects.[9] Anthocyanosides are thought to decrease vascular permeability and redistribute microvascu-

lar blood flow.[10] They are similar to some of the agents in grape seed.

The mechanism in diabetes may be related to the high chromium content in bilberry leaf (9 parts per million), but further research is needed to determine this.[50]

Side effects and drug interactions. Reported adverse effects have been mostly benign, including mild digestive distress, skin rashes, and drowsiness.[50] There are no known drug interactions. Because it may affect blood glucose, additive hypoglycemia may occur with secretagogues. If an alcoholic extract is used, there could be a disulfiram reaction (cramping, diaphoresis, and nausea if alcohol is ingested).[10] In animals, prolonged use and very high doses have resulted in toxicity, including initial cachexia and excitation and eventual death.[27]

Clinical studies. Despite enthusiasm during World War II about using bilberry preserves for improving night vision in Royal Air Force pilots,[9] bilberry has not had demonstrated efficacy in controlled trials.[48] Although its use has been suggested for lowering of blood glucose, there have been no human trials. In streptozotocin-induced diabetic rats, 4 days of bilberry leaf administration caused plasma glucose levels to consistently decrease by 26%.[51]

Clinical notes. There is potential benefit but very limited evidence that bilberry may improve conditions related to blood vessel function, such as varicose veins, cataracts, and other ocular diseases.

For the fruit, standard doses of the dried ripe berries are 20–60 g/day. Decoctions have also been prepared by placing 5–10 g mashed berries in cold water, simmering for 10 min, then straining. The form used in studies has been standardized to contain 25% anthocyanosides.[10] A tea is prepared using 1 g finely chopped dried leaf in 150 ml boiling water and steeping for 5–10 min.[10]

Milk Thistle

Milk thistle (Silybum marianum) is a member of the aster family (Asteraceae or Compositae), which also includes daisies and thistles.[52,53] Milk thistle has been used extensively for various hepatic disorders, including hepatotoxicity secondary to acute and chronic viral hepatitis, mushroom poisoning, and alcoholic cirrhosis. It has also been used to attenuate hepatotoxic effects of certain medications.[52] Recently, its use has been proposed in diabetes to diminish insulin resistance.[54]

Chemical constituents are found in the fruit, seeds, and leaves. Milk thistle contains silymarin, which is composed of three main constituents: silybin, silychristine, and silidianin. Silybin is thought to have the most potent biological activity.[53]

Proposed mechanism of action. There are several proposed mechanisms that may benefit patients with hepatic disease or impairment.[52] One is inhibition of hepatotoxin binding to hepatocyte membrane receptor sites, resulting in hepatocyte stabilization. Another is reduction of glutathione oxidation, which may deplete diminished glutathione levels in the liver and intestines. Milk thistle also has antioxidant activity to protect against toxic free radicals. Finally, it stimulates protein synthesis, which may lead to enhanced hepatocyte regeneration.

Milk thistle may benefit patients who have insulin resistance secondary to hepatic damage. One theory is that lipoperoxidation may affect patients with diabetes, and restoration of normal malondialdehyde concentrations may improve diabetes.[54]

Side effects and drug interactions. Reported dose-related (>1,500 mg/day) adverse effects include loose stools as a result of increased bile flow and secretion.[55] Patients with allergies to the Asteraceae or Compositae family may exhibit cross-allergenicity with milk thistle administration.[10] No adverse drug interactions have been reported with milk thistle. Beneficial interactions, however, have included reduction of hepatotoxicity associated with acetaminophen, antipsychotics, halothane, and alcohol.[52]

Clinical studies. Several studies have evaluated the impact of milk thistle on hepatic disease. These studies include acute viral hepatitis, mushroom poisoning, drug-induced hepatitis, chronic liver disease, and alcoholic liver disease.[53] However, these studies have been fraught with shortcomings. Many were open-label, involved small numbers of patients, used different doses, involved different severities of liver disease, lacked control groups, and lacked well-defined study endpoints.

Milk thistle was evaluated in a 12-month, randomized, open-label trial in 60 type 2 diabetic patients with cirrhosis.[54] All subjects used insulin. One group of 30 received 600 mg/day of silymarin, and the other group of 30 received a placebo for 12 months.

Mean FBG declined from 190 mg/dl at baseline to 165 mg/dl at 12 months ($P < 0.01$ vs. baseline). HbA_{1c} declined from 7.9% at baseline to 7.2% at 12 months ($P < 0.01$ vs. baseline). Mean daily insulin requirement decreased significantly from 55 units/day at baseline to 42 units/day at 12 months ($P < 0.01$ vs. baseline). Results were significant in the group of patients on silymarin, but not in the control group.

Clinical notes. Milk thistle may protect against hepatotoxicity by such agents as acetaminophen, antipsychotics, alcohol, and halothane. The typical dose for liver disease is 200 mg three times/day. Milk thistle extract should be standardized to contain 70% silymarin, which then contains 140 mg silymarin. Because phosphatidylcholine enhances oral absorption, preparations containing this ingredient may be dosed at 100 mg/day.[52] These doses differ from doses used in clinical studies, which have ranged from 280 to 800 mg/day.

Milk thistle's potential use for diabetes is very preliminary.

BIOLOGICAL PRODUCTS THAT MAY ADDRESS COMPLICATIONS OF DIABETES

γ Linolenic Acid

γ linolenic acid (GLA) is an ω-6 fatty acid. Although other sources of GLA include black currant and borage oil, the main source used in nutritional supplements is evening primrose oil.[9] GLA has been used to treat diabetic neuropathy, hyperlipidemia, mastitis, premenstrual syndrome, eczema, rheumatoid arthritis, and multiple sclerosis.[9]

Proposed mechanism of action. In the body, linoleic acid (LA) is converted to GLA via regulation by the enzyme δ-6-desaturase (D6D).[56] Two metabolites of GLA, dihomogammalinolenic acid (DGLA) and arachidonic acid (AA) are prostaglandin precursors that regulate the balance of platelet aggregation and maintain blood flow in small blood vessels.[56]

In diabetes, conversion of LA to GLA is thought to be impaired secondary to problems with D6D. Subsequent problems may occur, such as difficulty maintaining nerve membrane structure, nerve blood flow, and nerve conduction.[57] An exogenous

source of GLA bypasses the need for conversion of LA to GLA.

Side effects and drug interactions. Most adverse effects are mild and include headache and mild gastrointestinal (GI) complaints, such as bloating and loose stools.[10] There are reports of prolonged bleeding time and one case report of seizures.[9] Seizures may potentially occur if GLA is combined with phenothiazines because these drugs may lower the seizure threshold.[10]

Clinical studies. Two main clinical trials have evaluated GLA. One was a 6-month randomized, double-blind, placebo-controlled trial evaluating its effects on peripheral neuropathy in 22 patients with type 1 or type 2 diabetes.[58] Twelve patients received 360 mg/day GLA, and 10 patients received a placebo. At the end of 6 months, there was improvement in neuropathy symptom scores ($P < 0.001$) as well as other parameters of neuropathy in the GLA group. There was no significant change in HbA_{1c}.

Another trial was a year-long, multicenter, randomized, double-blind, placebo-controlled trial involving 111 patients with type 1 or type 2 diabetes.[59] Patients were given 480 mg/day GLA. The investigators reported significant improvement in 13 of 16 parameters of neuropathy. HbA_{1c} did not improve, but GLA response was better in those patients whose initial baseline HbA_{1c} was <10%.

Clinical notes. GLA derived from EPO may improve problems with nerve membrane structure, impulse conduction, and nerve blood flow. Since HbA_{1c} does not improve, benefit is not secondary to blood glucose control. Doses used to treat neuropathy are 360–480 mg/day. Some experts have stated that it may take several months to see results with GLA and that, for maximal absorption, it should be taken with food.

Although the initial data seem promising and GLA is relatively benign, its role in treating neuropathic complications requires more investigation.

Ginkgo Biloba

Ginkgo biloba is one of the world's oldest living tree species, dating back more than 200 million years.[9] Extracts from dried leaves of younger trees are used in complementary therapies. Active ingredients include flavonoids (ginkgo-flavone glycosides) and terpenoids, consisting of ginkgolides and bilobalides.[60]

Ginkgo biloba is one of the most widely used drugs in Germany. It is used for "cerebrovascular insufficiency" and dementia. In diabetes, ginkgo biloba may be of use in ameliorating peripheral circulatory problems, such as intermittent claudication.[61] There is also some evidence that it may benefit sexual dysfunction.[62]

Proposed mechanism of action. The flavone glycosides, including quercetin, kaempferol, and isorhamnetin, are thought to have antioxidant activity and inhibit platelet aggregation. The ginkgolides are thought to improve circulation and inhibit the platelet-activating factor. The bilobalides are thought to have neuroprotective properties.[9,10,60]

Side effects and drug interactions. Patients may experience transient headaches for the first 2–3 days of use. GI upset occurs in <1% of patients. Exposure to the fruit pulp may produce cross allergenicity with poison ivy. Eating the seeds may produce loss of consciousness and tonic-clonic seizures.[9] There have been case reports of subdural hematoma,[63] subarachnoid hemorrhage,[64] and bleeding from the margin of the iris.[65]

The main drug interaction is the potential for additive antiplatelet activity when combined with antiplatelet drugs, such as warfarin or aspirin or with herbs that also have antiplatelet activity, such as ginger, garlic, and feverfew.[10]

Clinical studies. Clinical studies have been done with products containing 24% flavone glycosides and 6% terpene lactones.[10] For intermittent claudication, different trials have found that ginkgo increases maximum walking distance and pain-free walking distance. A recent meta analysis revealed a significant effect on increased pain-free walking distance.[61] The weighted mean difference was 34 m.

Ginkgo was found to improve antidepressant-induced sexual dysfunction in an open-label trial.[62] Ginkgo has been reported to have a beneficial effect on erectile dysfunction by improving penile arterial blood flow.[66]

Clinical notes. Doses used range from 120 to 160 mg/day for peripheral vascular disease.[10] Ginkgo is administered in divided doses, usually two to three times/day. Administration for 6–8 weeks is required to determine benefit. The role for ginkgo in diabetes care is still preliminary.

Garlic

Garlic, a member of the lily family,[9] has been used in cooking for thousands of years. Garlic contains the sulfur-containing chemical constituent, alliin, which must be converted to allicin (the active form) by the enzyme allinase. When the garlic bulb is chewed or crushed, this reaction occurs.[9] Ajoene is formed by the acid-catalyzed reaction of two allicin molecules.

Commercial preparations usually contain allin, not allicin. Conversion requires allinase, which is unstable in stomach acids. Dried garlic preparations may be effective only if they are enteric-coated to prevent gastric acid breakdown and permit release in the small intestine. Fresh garlic is effective.[9,10]

Garlic is used to treat hyperlipidemia and hypertension, for cancer prevention, and for other antibacterial activity. Although evidence is preliminary, garlic may be useful in diabetes.[67]

Proposed mechanism of action. Allicin has antibacterial and antioxidant activity. It may possibly increase blood levels of catylase and glutathione peroxidase activity. Ajoene decreases the activity of factors needed for lipid synthesis by reducing the thiol group in coenzyme A and HMG CoA reductase and also by oxidizing NADPH. Ajoene has antiplatelet activity and interferes with thromboxane synthesis and decreases platelet aggregation.[9]

Researchers have noted that garlic use may be associated with increased serum insulin and improved liver glycogen storage.[67] A constituent of garlic, allylpropyl disulfide, may reduce blood glucose and increase insulin.[10]

Side effects and drug interactions. Side effects include breath odor, mouth and GI burning or irritation, heartburn, flatulence, and rare topical reactions. There are cases of spontaneous spinal epidural hematoma[68] and excessive bleeding.[69]

Potential drug interactions may occur if a patient is taking antiplatelet agents, such as warfarin or aspirin.[10] Additive anticoagulant effects may occur when combined with herbal products that have antiplatelet activity, such as ginkgo, ginger, and feverfew.

Clinical studies. A recently published meta-analysis included trials from previously published meta analyses and newer trials.[70] The results revealed that garlic reduced total cho-

lesterol more than did placebo ($P < 0.01$). The result was more modest than in previous studies. Mean total cholesterol decrease was 15.7 mg/dl.

In mild hypertension, a 1994 meta-analysis indicated that mean systolic blood pressure was 7.7 mmHg lower than with placebo, and diastolic blood pressure was 5 mmHg lower.[71] However, only three of the trials were conducted in hypertensive subjects. Seven of the eight trials in the meta-analysis compared garlic to placebo. Three of the trials found a significant reduction in systolic blood pressure, and four trials showed a significant reduction in diastolic blood pressure.

Clinical notes. Although lipid lowering has been shown with garlic use, the results are less impressive than with traditional agents. Although total cholesterol is lowered, there is less evidence for benefit to LDL, triglycerides, or HDL cholesterol. Garlic may not provide the aggressive lipid lowering that is recommended for patients with diabetes. Likewise, patients with diabetes need more aggressive antihypertensive effects than garlic may provide.

The dose to treat hyperlipidemia and hypertension is 600–900 mg/day in divided doses.[10] For fresh garlic, the dose is one clove (4 g) taken once/day.[10] Dried garlic powder preparations standardized to 1.3% allicin content have been used in studies. These preparations should be enteric-coated to prevent breakdown by stomach acids.[10]

α-Lipoic Acid

α-lipoic acid (ALA), also known as thioctic acid, is a disulfide compound synthesized in the liver.[72] It functions as a cofactor in enzyme complexes such as pyruvate dehydrogenase, where it assists in the conversion of pyruvic acid to acetyl-coenzyme A in the oxidative metabolism of glucose.[72]

In vitro and animal research indicates that elevated glucose levels may increase free radical-mediated oxidation, which in turn is strongly implicated in the pathogenesis of diabetes-related neuropathy.[73] Because ALA may decrease oxidative stress (in part caused by increased blood glucose levels), it may help minimize diabetes complications. ALA has been used in Germany for decades to treat peripheral neuropathy.

Proposed mechanism of action. ALA is readily converted to its reduced form, dihydrolipoic acid (DHLA).[18] ALA and DHLA are both potent antioxidants and have three distinct actions: *1*) free radical scavenging activity; *2*) regeneration of endogenous antioxidants such as vitamin C, vitamin E, and glutathione; and *3*) metal chelating activity.[73]

Side effects and drug interactions. Serious side effects have not been reported. ALA may produce GI side effects and possible allergic skin conditions.[74] ALA may potentially result in additive hypoglycemia when combined with hypoglycemic agents.[75]

Clinical studies. ALA was studied in the ALADIN (Alpha Lipoic Acid in Diabetic Neuropathy) trials. The first trial[74] was a randomized, double-blind, placebo-controlled trial in 260 type 2 diabetic patients with symptomatic peripheral neuropathy. For 3 weeks, patients were administered placebo or intravenous (IV) ALA (100, 600, or 1,200 mg) daily. Total symptom scores of neuropathy decreased significantly for all three ALA doses versus placebo ($P < 0.05$). Burning, paresthesia, and numbness decreased significantly in patients on 600 and 1,200 mg/day versus placebo ($P < 0.05$). Pain scores decreased significantly only in the 600 mg/day versus placebo group ($P < 0.05$). However, both the 600- and 1,200-mg doses decreased Hamburg Pain Adjective List scores ($P < 0.01$ vs. placebo). The Neuropathy Disability Score decreased but was significant only for the 1,200-mg group versus the placebo group ($P = 0.030$).

The second ALADIN trial (ALADIN II) was a randomized, double-blind, placebo-controlled 2-year trial in 65 patients with type 1 or type 2 diabetes and polyneuropathy symptoms.[76] Following administration of placebo, 600 mg, or 1,200 mg/day IV for 5 days, patients were then randomized to oral placebo, 600 mg, or 1,200 mg/day for 2 years. Mean sural nerve conduction velocity changes were significant only for 600 and 1,200 mg versus placebo ($P < 0.05$). Sural sensory nerve action potential scores decreased significantly only for 600 mg versus placebo ($P < 0.05$). Tibial motor nerve conduction velocity changes were significant only for 1,200 mg versus placebo ($P < 0.05$).

ALADIN III[77] was a randomized, double-blind, placebo-controlled trial in 503 patients with type 2 diabetes. One group was given 600 mg IV/day of ALA for 3 weeks, and then subjects were randomized to oral ALA, 600 mg three times daily, or placebo for 6 months. The other group was given daily IV placebo for 3 weeks followed by oral placebo for 6 months. Mean baseline neuropathic impairment scores decreased after 19 days in the two ALA groups versus placebo ($P = 0.02$). After 7 months, however, differences were not significant between the groups. The authors suggested that lack of effect in this trial, as opposed to the earlier trials, might have been due to intercenter variability in symptom scoring.

Clinical notes. There is no information on the prevention of neuropathy with ALA. The clinical significance of the reported improvement in different parameters of neuropathy in the ALADIN studies[74,76,77] may be enhanced quality of life for patients who experience neuropathy.

Long-term trials are necessary to determine whether ALA slows progression of neuropathy or merely improves neuropathy symptoms. The Neurological Assessment of Thioctic Acid in Neuropathy Study (NATHAN) is an ongoing multicenter trial in Europe and North America to evaluate the ability of oral ALA to slow progression of neuropathy in diabetes.[78]

Typical oral doses of ALA are 600–800 mg/day.[10] Although intravenously administered ALA has been shown to be effective when used in short-term clinical trials,[74] it is not a practical form for supplementation.

The American Diabetes Association does not sanction use of ALA.

Conclusions

Although biological complementary therapies have been studied in human clinical trials, there are many problems with study design, study endpoints, numbers of patients, and study duration. There is insufficient evidence to recommend generalized use for patients with diabetes. Furthermore, these products have many side effects and may potentially interact with traditional diabetes medications.

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