Objective: To provide pharmacists with practical information to guide consumers in their choices of herbal products and dietary supplements for the management of type 2 diabetes mellitus (T2DM) and its comorbid disease states.

Summary: The herbal and dietary supplement market has grown exponentially over the past decade as Americans increasingly use such agents for generalized health and the prevention and treatment of chronic disease states.1 Pharmacist advice is often requested on the use of these agents for the management of T2DM; however, this is an area that has insufficient evidence to support confident recommendations. Many published studies involving herbal agents and dietary supplements are small and poorly designed, with heterogeneous results. Pharmacists should be aware of the safety and efficacy data available for these agents, recognize potential drug interactions, and identify acceptable manufactured products.

Conclusion: The strongest scientific evidence for blood glucose lowering effect is associated with alpha-lipoic acid and fenugreek. There is also good evidence supporting the use of ivy gourd, gymnema, and vitamin E for management of hyperglycemia; however, caution should be used when recommending vitamin E. Pharmacists should advise consumers to disclose use of any of these products to all of their health care providers.

Keywords: Diabetes, herbal supplements, dietary supplements, botanicals

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Learning objectives
At the conclusion of this knowledge-based activity, the pharmacist will be able to:
• Identify natural products and dietary supplements associated with an anti-hyperglycemic effect.
• Describe safety and efficacy data associated with the most commonly used agents for diabetes management.
• Identify important drug–drug interactions associated with the most commonly used agents for diabetes management.
• List three items that should clearly be identified on the package labeling before recommending a particular herbal or dietary supplement.
Introduction

The use of herbals and dietary supplements for generalized health and the prevention and treatment of chronic disease states is increasing throughout the United States. The most recent National Health and Nutrition Examination Survey (NHANES) data (2003–06) indicates that approximately 53% of Americans aged 20 years and older use dietary supplements, representing a 10% increase in use from the 1988–94 data. 

Similarly, a secondary analysis of the complementary and alternative medicine (CAM) supplement to the 2002 National Health Interview Survey (NHIS) found that 57.3% of adult dietary supplement users took such products to treat a specific medical condition in the previous 12 months. According to a 2008 study, individuals with diabetes are 1.6 times more likely to use alternatives to traditional medicine compared with those without the disease.

Access to herbal and dietary supplements was greatly enhanced by passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA). Prior to DSHEA, dietary supplements were held to the same regulatory requirements as other foods. Now, the manufacturer of a dietary supplement is responsible for ensuring product safety prior to marketing, while FDA is tasked with taking action against unapproved natural products compared with respondents without diabetes (15.7% vs. 19.2%). Those with diabetes who did use CAM mostly did so for non-diabetes conditions.

With more available information, it is possible that one or more of these agents may become an element of conventional treatment for patients with diabetes. Metformin—now a cornerstone of diabetes prevention and treatment—is an example of how such a transition can occur. Metformin was discovered from use of the medicinal plant Galega officinalis to treat diabetes. Based on the recommendation of the World Health Organization Expert Committee on Diabetes, efforts are currently underway to determine the utility of other traditional medicinal herbs in diabetes care.

In a study by Yeh et al, CAM use in patients with diabetes included prayer and spiritual practice (28%), herbal remedies (7%), and commercial diets (6%). In a separate study by Bell et al, a greater number of individuals with diabetes were found to use CAM approaches compared with those without the disease (73% vs. 61%); however, a significantly lower number of respondents with diabetes used non-vitamin, non-mineral natural products compared with respondents without diabetes (15.7% vs. 19.2%). Those with diabetes who did use CAM mostly did so for non-diabetes conditions. These findings underscore the need to determine the actual use of herbal remedies for diabetes care, as well as anticipated and actual outcomes. This review focuses on practical information to aid pharmacists in guiding consumers on the use of herbals and dietary supplements for managing type 2 diabetes mellitus (T2DM) and its comorbid disease states.
**Herbal products**

**Bitter melon (Momordica charantia)**

Bitter melon is also known as bitter gourd, karela, or balsam pear. It is sometimes referred to as “vegetable insulin” because its extract components share structural similarities with animal insulin. Purported mechanisms include enhanced pancreatic insulin secretion and decreased hepatic gluconeogenesis.

**Safety:** Based on animal studies, isolated proteins from bitter melon have abortifacient properties; therefore, bitter melon should be used with caution in women of childbearing age. Bitter melon should be avoided in nursing women, children, and those with allergies to foods in the gourd or melon family. Additionally, ingestion of bitter melon seeds may cause fumism—the onset of hemolytic anemia—in those with glucose-6-phosphate dehydrogenase (G6PDH) deficiency.

**Known drug interactions:** Bitter melon may be a p-glycoprotein inhibitor; concomitant use with digoxin should be avoided.

**Efficacy:** Bitter melon has shown hypoglycemic effects in various animal models, some low-quality human trials, and one case report. A randomized controlled trial by Dans et al. compared bitter melon extract (1000 mg three times daily) with placebo in patients with uncontrolled T2DM (glycosylated hemoglobin [A1C] levels of 7%–9%). The mean difference in treatment for A1C was 0.22% in favor of bitter melon (non-significant); however, the study sample size was only 40 participants and power was not met.

Fuangchan et al. published a study comparing dried bitter melon fruit powder doses of 500 mg/day, 1000 mg/day, and 2000 mg/day with metformin 1000 mg/day. The four-week study based efficacy on lowered fructosamine levels, a measure of glycemic control over the past 2–3 weeks. Of the bitter melon doses, only the 2000 mg/day dose showed significant reduction in mean fructosamine levels, but there was no effect on fasting or postprandial blood glucose levels. Bitter melon reduction in fructosamine levels was less than that seen with a suboptimal metformin dose.

Bitter melon in doses of 2 grams per day may have an effect on long-term blood glucose lowering, but immediate effects have not been observed.

**Burdock (Arctium lappa)**

Burdock, which is rooted in traditional Chinese medicine, has been examined for uses as an anti-inflammatory, anticancer, antidiabetes, antimicrobial, and antiviral agent. Burdock root and fruit have been suggested as the parts of the plant that likely contribute the most to producing hypoglycemic effects. The root contains sitosterol-beta-D-glucopyranoside, which is thought to have alpha-glucosidase inhibitor activity, and inulin, which helps to regulate blood glucose levels. Total lignin from the burdock fruit has suggested antidiabetic activity in animal studies.

**Safety:** Different parts of the burdock plant contain varying levels of pectin complex. Avoid use in individuals with allergy or intolerance to pectin. Burdock should also be avoided in patients with allergies to ragweed, chrysanthemums, marigolds, or daisies. Animal studies suggest increased bleeding risk with burdock use; therefore, recommend caution with concomitant use of anticoagulants or antiplatelet agents. Of greatest concern is that burdock can be confused with belladonna alkaloids during harvesting, and atropine-like effects have been seen following the consumption of contaminated burdock. Burdock itself does not have atropine-like effects.

**Known drug interactions:** Burdock tinctures may contain high concentrations of alcohol, which may induce vomiting if combined with disulfiram or metronidazole.

**Efficacy:** Animal data and weak human data suggest the root or fruit of burdock may produce hypoglycemic effects, but reliable data is lacking. Further studies are needed before recommending burdock for the management of T2DM.

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**Case study 1**

A 28-year-old obese female with T2DM requests an herbal supplement to use in addition to metformin for glycemic control. She has no other disease states but is allergic to grass, trees, and ragweed. Name two herbal supplements you would avoid recommending in this patient for glycemic control.

Bitter melon should be avoided in all women of childbearing age because of the risk of miscarriage. Additionally, burdock should not be recommended at this time to any patient for glycemic control given the risk of contamination with belladonna alkaloids. Burdock should also be avoided in patients allergic to ragweed, chrysanthemums, marigolds, daisies, or pectin.

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**Cinnamon (Cinnamomum cassia)**

Cinnamon, also sometimes referred to as Chinese cinnamon, is derived from the dried inner bark of evergreen trees grown in the tropical climates of Asia. The active ingredients in cinnamon include cinnamaldehyde and procyanindin type-A polymers. It is purported that these constituents enhance insulin sensitivity by improving glucose uptake and glycogen synthesis.

**Safety:** When used in natural food sources, cinnamon appears to be safe. In clinical trials, gastrointestinal disorders were the most reported adverse effect associated with cinnamon use. It should be noted that cinnamon is a top food allergen, so caution should be exercised when recommending its use among mass populations.

**Known drug interactions:** Cinnamon contains a coumarin component, so caution should be used when recommending with concurrent administration of anticoagulants.

**Efficacy:** Results of randomized trials from human and animal studies have indicated hypoglycemic effects; however, the results have been conflicting. To date, studies of patients with T2DM have involved the administration of 1, 3, or 6 grams per day of cinnamon in divided doses.

While there is currently insufficient data to recommend cinnamon for any human condition, its use in the treatment of T2DM seems to be the most desired field of research. The use of cinnamon increased substantially after 2003 when Khan et al. demonstrated a lowering of blood glucose values in patients with T2DM. Consequently, patients began questioning if cinnamon may be an appropriate alternative.
or supplement for diabetes management.

Allen et al. conducted a systematic review and meta-analysis of randomized trials evaluating cinnamon (monotherapy or in combination) in patients with T2DM. A total of 10 studies involving 543 participants met eligibility criteria. Doses of aqueous cinnamon extract or raw cinnamon powder ranged from 120 mg/day to 6 g/day over a period of 4–18 weeks. Cinnamon was associated with a statistically significant reduction in fasting plasma glucose levels of 24.59 mg/dL. High degrees of heterogeneity were present for this, but no statistically significant effect was seen in A1C levels (−0.16%).

Leach and Kumar conducted a Cochrane Review analysis of randomized controlled trials using cinnamon as monotherapy for type 1 diabetes (T1DM) or T2DM. A total of 10 studies met eligibility criteria (n = 577 participants), with only 2 of the studies different from those evaluated in the Allen review. Cinnamon cassia was the predominant form of cinnamon used (mean dose of 2 g/d) for a period of 4–16 weeks. In the meta-analysis, no conclusions could be made regarding the efficacy of cinnamon on fasting blood glucose levels. Of the six trials reporting A1C levels (n = 405), there was no statistically significant difference in A1C levels (mean difference −0.06%).

Further studies are needed before recommending cinnamon as an agent for glycemic control.

**Dandelion (Taraxacum officinale)**

Dandelion is a member of the Asteraceae family. Found growing wild in meadows and pastures of temperate zones, it provides fiber, potassium, iron, calcium, magnesium, phosphorus, thiamine, and riboflavin when ingested. Dandelion has traditionally been used to treat gastrointestinal disorders. FDA has approved dandelion fluid extract and solid dandelion root extract as food additives; they are currently used as salad ingredients and coffee substitutes.

**Safety:** Dandelion is considered likely safe when taken orally in amounts found naturally in foods, earning FDA’s “generally recognized as safe” designation. It has been well-tolerated in human studies, with the most commonly reported adverse effects being dermatologic in nature, following direct contact. However, safety data beyond 4 months of use is lacking. Use should be avoided in individuals who are allergic to dandelion, honey, chamomile, chrysanthemums, or any member of the Asteraceae family.

A theoretical concern is that dandelion stimulates bile secretion and therefore should not be used in individuals with liver or gallbladder disease; however, supporting data for this is lacking. The prudent approach at this time would be to avoid recommending dandelion if liver or gallbladder disease is present.

**Known drug interactions:** Dandelion may cause increased gastric acid secretion; therefore, it may reduce the effectiveness of antacids. Dandelion may also increase the risk of bleeding, so caution is recommended with concomitant use of anticoagulants or antiplatelet agents.

**Fenugreek (Trigonella foenum-graecum)**

Fenugreek is a fiber-rich plant that is a member of the Fabaceae family. It is commonly used for glycemic control in foreign countries such as Saudi Arabia and Canada. The mechanism of action is thought to be a delay in gastric emptying, slowed carbohydrate absorption, and increased insulin sensitivity of the tissues. Fenugreek seeds reportedly increase glucose-dependent insulin secretion.

**Safety:** The most commonly reported adverse effects of fenugreek are gastrointestinal, including dyspepsia and abdominal distention. Fenugreek also has a blood thinning effect and may cause hypokalemia.

Fenugreek should not be recommended for use in individuals allergic to members of the Fabaceae family (peanuts, chickpeas, soybeans, or green peas).

**Known drug interactions:** Because it is rich in fiber, fenugreek may interfere with the absorption of some oral medications. Therefore, it is recommended that the coadministration of oral medications and fenugreek be spaced out by at least 2 hours. Additionally, caution should be exercised with concomitant use of potassium-depleting agents.

**Efficacy:** Daily doses of 5–100 grams of fenugreek seed powder have been shown to improve fasting blood glucose, postprandial glucose, and A1C levels in patients with T2DM.

From a pooled analysis, Suksomboon et al. determined that fenugreek had a statistically significant decrease in A1C (1.13%), but no effect on fasting blood glucose.

Neelakatan et al. conducted a meta-analysis to assess the effect of fenugreek on glucose homeostasis; 10 trials met inclusion criteria, but only 8 were selective for patients with T2DM. Results of the meta-analysis included significant reductions in fasting blood glucose (−0.96 mmol/L), postprandial blood glucose (−2.19 mmol/L; 7 trials), and A1C levels (−0.85%; 3 trials). Significant reductions in glycemic markers were only found with medium to high doses of fenugreek seed powder (≥5 g/d).

Fenugreek seed powder in daily doses of at least 5 grams appears to be a safe and effective option for glycemic control in persons with T2DM.

**Ginseng—Korean red (Panax ginseng) and American (Panax quinquefolius)**

While several species of ginseng are used in herbal products, the most common are of the *Panax* genus. Other species of ginseng from different botanical families (e.g., Siberian) are sometimes sold as less expensive alternatives.
However, they lack the efficacy data associated with the Panax genus.16

The glucose lowering effect of Panax is attributed to its ginsenosides, but the peptidoglycan and glycan constituents have also shown beneficial effects.1 However, there is great difficulty in standardizing Panax ginseng products. Currently, there are more than 30 identified ginsenosides, so there may be considerable variability in the composition of marketed ginseng products.1

Safety: Insomnia is the most commonly reported side effect. Anxiety, headache, and tachycardia have also been reported.5

Known drug interactions: Caution should be exercised with concomitant use of agents that increase bleeding.16 Ginseng has also been linked to a plethora of potential drug interactions (e.g., antihypertensives, antidepressants, pain relievers, antibiotics); however, data is lacking to definitively support these interactions.16

Efficacy: Vuksan et al.1 evaluated the acute and chronic effects of American and Korean red ginsengs using a standardized ginsenoside component administered at specific times. The study found that doses of 1–9 grams of American ginseng were equally effective in the acute and long-term reduction of postprandial hyperglycemia (~15–20%). Chronic antihyperglycemic efficacy of American ginseng was evaluated using 1 gram of ginseng extract 40 minutes before each meal (3 g/d). Similarly, the administration of 2 grams of Korean red ginseng rootlets 40 minutes before each meal (6 g/d) demonstrated acute and chronic antihyperglycemic efficacy. Administration time of at least 40 minutes prior to the meal was significant.

A separate study evaluating the safety and efficacy of Korean red ginseng observed acute efficacy for glycemic control, but did not see any long-term effects as measured by A1C levels.28

High variability in the composition of ginseng products is linked to the inconsistent efficacy observed in studies, with no standardization existing at this time for the different ginsenosides and their ratios.1 Limited efficacy data and lack of standardization limit the recommendation of Panax ginseng products for glycemic control.

Gymnema (Gymnema sylvestre)
Gymnema is a woody, climbing plant native to the tropical forests of central and southern India.8 In Hindu folklore, chewing gymnema leaves results in the inability to taste sweets. It is therefore also known as “gurmar,” which means “destroyer of sugar” in Hindi.8 The exact mechanism of action is unknown, but suggested mechanisms include enhanced insulin secretion, beta cell regeneration, and enhanced peripheral glucose utilization.8

Safety: Based on limited trial data, gymnema appears to be safe, with the most notable side effect being taste alteration.8 Patients may experience diminished perception of sweet taste and enhanced perception of bitter taste.

Known drug interactions: Gymnema may enhance the lipid-lowering effects of antilipemic agents and the weight loss effects of antiobesity agents.16

Efficacy: Animal studies have demonstrated glucose-lowering effects in animals with residual pancreatic function, but not in pancreatectomized animals; however, gymnema has demonstrated efficacy in human trials in both patients with T1DM and T2DM.8

Baskaran et al.29 conducted a non-randomized study of 47 patients with T2DM. For 18–20 months, 22 of the patients were administered 400 mg/day of GS4, an extract from gymnema sylvestre leaves, in combination with oral hypoglycemic agents. Statistically significant reductions in fasting blood glucose values (~2.78 mmol/L) and A1C levels (~3.43%) were reported. Almost all patients in the treatment group required dose reduction or discontinuation of sulfonylureas within several weeks (unspecified time). The study authors also observed elevations in serum insulin levels in the fasting and postprandial state in those participants treated with GS4.

It may be safe to recommend gymnema for glycemic lowering in T2M. However, further well-controlled trials need to be conducted in this population to establish safety and efficacy.

Ivy gourd (Coccinia indica)
Ivy gourd is an aggressive climbing vine found in tropical areas.16 Both human and animal studies have found that the fruit and leaves of ivy gourd can lead to reductions in fasting and postprandial blood glucose values. Ivy gourd is a source of fiber, which may account for its ability to lower blood glucose levels, but it is also speculated to possess insulin-like effects.12,16 Ivy gourd’s exact mechanism of action remains unclear.8

Safety: Published clinical trials report a lack of adverse events associated with the use of ivy gourd.16 In a 2008 study using an alcoholic extract of ivy gourd, participants experienced mild disturbance of the gastrointestinal tract (abdominal distention, flatulence, constipation, and gastritis). However, more participants in the placebo group experienced these symptoms than those in the intervention group, and the symptoms resolved within 1 week.30

Known drug interactions: No known drug interactions exist.16

Efficacy: Evidence for the potential efficacy of ivy gourd in lowering blood glucose dates back to a 1979 study conducted in Bangladesh, which found that 1800 mg/day of ivy gourd decreased both fasting and postprandial blood glucose values, with no reported side effects.8,31 A case series published by Kamble et al.22 compared use of 6 g/day of ivy gourd to that of chlorpropamide and found that the two treatments were similar in their ability to lower fasting and postprandial blood glucose levels.

Additional data are needed prior to recommending ivy gourd for treatment of T2DM.

Nopal (Opuntia streptacantha)
Prickly pear cactus, known as nopal to the Mexican community, has high soluble fiber and pectin content in its fresh state,15 which may affect intestinal glucose uptake.8

Safety: Diarrhea and increased stool volume have been
reported with nopal use, as have allergic nasal inflammation and asthma. Nopal is likely safe when used as a food source.

Known drug interactions: Nopal may increase bleeding when combined with anticoagulants or antiplatelet agents. Additionally, nopal may cause increased drug levels of agents metabolized through the cytochrome P450 enzyme system. Nopal may also help reduce cholesterol; thus an additive effect is possible when combined with cholesterol-lowering agents.

Efficacy: The leaves and stem of nopal have been studied for glycemic effects, with nopal shown to decrease glucose in both pancreatectomized and nonpancreatectomized animals. Additionally, doses of 100–600 grams/day have provided hypoglycemic effects in individuals with T2DM.

Studies are generally limited on this readily available plant. However, given the lack of significant side effects seen in trials and the possible glucose-lowering effect of nopal, it can safely be recommended for consumption as a food source.

Onion (Allium cepum)

Onion is part of the Allium species and contains allyl propyl disulphide. It is suggested that onion’s hypoglycemic properties are attributable to enhanced pancreatic insulin secretion and/or improved hepatic storage of glycogen.

Safety: Onion is likely safe when consumed as part of a normal diet, though increased dietary intake may induce heartburn or dyspepsia. Onion has resulted in lowered blood pressure in patients both with and without hypertension; therefore, its increased intake should be accompanied by cautious monitoring of blood pressure.

Known drug interactions: P-glycoprotein substrates and medications metabolized by the cytochrome P450 enzyme system may interact with onion. Additionally, onion may increase bleeding risk when combined with anticoagulants or antiplatelet therapy.

Efficacy: Onion has reduced fasting and postprandial blood glucose levels in both animal (rabbit) and human studies. Given as a single orally administered dose of 25, 50, 100, or 200 grams of aqueous onion extract (either boiled or raw), onion lowered fasting blood glucose levels in a dose-dependent manner and was comparable to tolbutamide—a first-generation secretagogue. Additionally, an onion diet of 3 x 20 grams of fresh onion decreased or maintained blood glucose compared with the placebo group [9.1% (±0.51) to 10.5% (±0.59)]. As in previously published studies, Anderson et al. observed a “second meal effect” in the psyllium-treated group, with psyllium doses taken before morning meals resulting in statistically significant lower post-lunch postprandial blood glucose levels compared with the placebo group (−19.2%).

Ziai et al. evaluated the glycemic benefit of psyllium in persons with T2DM in a double-blind, placebo-controlled study. Psyllium dosing, dosing schedule, and study duration were identical to the study conducted by Anderson et al. Of the 49 enrolled patients, 36 completed the study, with no attrition in the treatment group due to adverse effects. A statistically significant decrease in A1C levels from baseline were reported in the psyllium-treated group [10.5% (±0.73) to 8.9% (±0.23)], while an increase was seen in the placebo-treated group [9.1% (±0.51) to 10.5% (±0.59)].

When either added to one’s regularly consumed diet or used as fiber supplementation, psyllium may help benefit glycemic control.

Dietary supplements

Alpha-lipoic acid

Alpha-lipoic acid (ALA) is an endogenous dithiol antioxidant that is naturally synthesized in the body. ALA acts as an antioxidant and coenzyme, and evidence exists that it may aid in the treatment of both T2DM and diabetic neuropathy.

Safety: ALA is generally well tolerated when daily doses do not exceed 1200–1800 mg. Common adverse effects include nausea, vomiting, and vertigo, especially at the higher dose ranges (1200 mg or above).

Use of ALA is a risk factor for the development of insulin autoimmune syndrome (IAS), also known as Hirata disease, a rare cause of hypoglycemia due to the production of auto-
antibodies to insulin in individuals who have not previously been treated with insulin. Additional risk factors for IAS include the use of sulfonylurea drugs (e.g., methimazole, mercaptopropionyl glycine, and glutathione). Risk is also higher in persons from East Asia and certain patients of native North American descent.

**Known drug interactions:** Significant drug interactions have not been noted with ALA.

**Efficacy:** ALA administered orally or via IV may improve insulin sensitivity and glucose disposal in persons with T2DM.41–46

Mazloom et al.46 conducted a randomized, placebo-controlled study to assess the effect of ALA on A1C and blood glucose levels in 70 patients with T2DM. Patients remained on oral diabetes medications and were randomized to receive 300 mg ALA or placebo three times daily for 8 weeks. Compared with baseline, patients in the ALA group showed significant reductions in mean fasting blood glucose levels and 2-hour postprandial glucose levels. No significant difference between ALA and placebo treatment groups was observed.

A separate randomized, placebo-controlled trial by Blum et al.61 performed a meta-analysis of two randomized trials to evaluate the cardiovascular protection effects of vitamin E supplementation in patients with T2DM and haptoglobin 2-2 genotype (a cardiovascular disease risk marker in diabetes). Patients were administered 400 IU daily of vitamin E. Endpoints included nonfatal myocardial infarction, stroke, and cardiovascular disease death, in addition to a composite endpoint. A protective effect of vitamin E was statistically significant for all endpoints except stroke. Detailed information about methodology of the trials was not included in the meta-analysis. Vardi et al.63 confirmed a possible benefit of vitamin E in patients with T2DM and haptoglobin 2-2 genotype.

In a meta-analysis performed by Suksomboon et al., vitamin E supplementation did not improve glycemic control in the overall group of patients with T2DM. However, vitamin E did improve glycemic control in patients with inadequate glycemic control at baseline (A1C ≥8%) and baseline serum vitamin E levels below normal ranges.
Other data suggest that vitamin E has no effect on serum glucose, A1C, or fructosamine levels.54,64-66 In the HOPE trial, treatment with vitamin E for an average of 4.5 years had no effect on cardiovascular outcomes.65

Some experts believe that vitamin E supplementation in the form of alpha-tocopherol rather than gamma-tocopherol may be a factor in the observable negative effects or lack of effects reported.16 Gamma-tocopherol is believed to have more antioxidant effects compared with alpha-tocopherol.

Caution should be exercised prior to recommending vitamin E to patients because of possible adverse effects and the lack of beneficial data.

**Chromium**

Chromium is an essential element in the metabolism of carbohydrates, lipids, and proteins.16 Chromium picolinate, the most common synthetic chromium product evaluated in published literature, is thought to be more completely absorbed and have a greater bioavailability than other chromium formulations.69,70 Chromium picolinate has been administered at doses ranging from 200 to 1400 mcg/day for a period of 6 weeks to 6 months. Other doses of varying forms of chromium have also been studied, including chromium chloride, chromium-enriched yeast, and brewer’s yeast.

**Safety:** Trivalent chromium, typically found in food and supplements, appears to be safe, with very low toxicity.16 Many of the studies assessing the effects of chromium on patients with T2DM reported either no adverse events or such minimal effects as nausea, vomiting, constipation, headache, and vertigo.16,70,71

Chromium is likely safe when used appropriately, although shortened QTc intervals have been reported.16

**Known drug interactions:** Theoretically, chromium may interact with selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, antiparkinsonian agents, and central nervous system stimulants.16 Chromium picolinate may affect the central nervous system metabolism of dopamine, serotonin, and norepinephrine. Additionally, administration of H2 blockers may inhibit the absorption of chromium. Administration of levothyroxine sodium and chromium should be separated by several hours.

**Efficacy:** Chromium use in patients with T2DM has been associated with beneficial effects on glucose, lipid metabolism, and insulin sensitivity.45,68,69,72-74 Balk et al.19 conducted a systematic review of randomized controlled trials evaluating the effect of chromium supplementation on glucose metabolism and lipid profile parameters. A total of 41 studies comprising 431 patients with either T2DM or glucose intolerance met the eligibility criteria. Overall, chromium supplementation in patients with T2DM proved statistically significant in reducing A1C by 0.6% and fasting glucose by −1.0 mmol/L; however, lipids were not improved. None of the included studies reported differences in patients with glucose tolerance.

However, the results of other studies are inconsistent with these findings.70,71,73,76 Althuis et al.77 conducted a systematic review and meta-analysis of 15 randomized controlled trials to determine the effect of chromium on glucose and insulin responses. There was no association between chromium and glucose or insulin concentration in subjects without diabetes, while data included in the analysis for patients with diabetes were inconclusive. Kleefstra et al.71 reported similar negative results in a study evaluating chromium supplementation in patients with T2DM on oral agents. Many of the studies evaluated were small and lacked defined methodology or information critical to assessing the trial.

Additional research with more defined endpoints and better methodology should be conducted prior to recommending chromium for the management of T2DM.

**Pyridoxine/vitamin B6**

Pyridoxine (Vitamin B6) is required for the synthesis of serotonin and norepinephrine, as well as for myelin formation.16 Pyridoxine supplementation has been assessed for improvement of glucose metabolism and in the treatment of diabetic neuropathy.

**Safety:** Pyridoxine is likely safe when used orally in doses within the recommended dietary allowance.16 Doses greater than 200 mg should be avoided, as reversible neuropathy has been reported with high doses.16,78

**Known drug interactions:** Due to an additive hypertensive effect, pyridoxine should not be used in combination with other antihypertensives or in patients with cardiovascular conditions.16 Patients treated for Parkinson disease should use caution before taking additional pyridoxine, as it may enhance the metabolism of levodopa when levodopa is taken as a single agent.

**Efficacy:** Pyridoxine may have a role in the treatment of diabetic neuropathy.38,78-80 In combination with thiamine 25 mg daily, pyridoxine 50 mg may reduce the severity of symptoms in patients with diabetic neuropathy.38,78 Abbas et al.80 assessed the effect of pyridoxine 50 mg and thiamine 25 mg daily in patients with diabetes. A total of 100 control patients received a tablet identical to that provided to the treatment group but containing only 1 mg of pyridoxine and 1 mg of thiamine. Severity of peripheral neuropathy symptoms decreased in 48.9% of patients in the treatment group, compared with 11.4% in the control group. Because patients’ pyridoxine levels were not reported, it is difficult to determine the role of pyridoxine supplementation in the trial. Conflicting evidence for use of pyridoxine in the management of neuropathy in T2DM patients also exists.38,78

Researchers have also evaluated the use of pyridoxine for impaired glucose tolerance in nonpregnant patients with pyridoxine deficiency, with supplementation not found to significantly improve either glucose tolerance or insulin response to glucose.89 This finding was affirmed by another study in which 7 of 13 included patients had a pyridoxine deficiency.52

At this time, pyridoxine should not be routinely recommended for glycemic control or peripheral neuropathy to patients without pyridoxine deficiency. Additional studies are required.

**Selenium**

Selenium is an essential trace mineral found in soil, water,
and some foods. It functions as a cofactor for the antioxidant enzymes.

**Safety:** Selenium should not be used in patients on hemodialysis or immunosuppressants, or in patients with hyperlipidemia, hypothyroidism, or high risk for development of T2DM.

**Known drug interactions:** Possible drug interactions with selenium include HMG-CoA reductase inhibitors, barbiturates, and erythropoietin.

**Efficacy:** Data do not support use of selenium for the treatment of T2DM. Interestingly, both low concentrations of selenium in toenails and high serum levels of selenium have been associated with an increased risk for the development of T2DM. In one secondary analysis, patients who took selenium 200 mcg daily for an average of 7.7 years had a significantly increased risk for T2DM.

Selenium should not be recommended for the treatment of T2DM.

### Case study 2

A 74-year-old male patient with T2DM and benign prostatic hyperplasia (BPH) is currently taking selenium. He heard that selenium may be helpful in controlling his BPH as well as his diabetes. His diabetes is well controlled with his current regimen, which includes metformin. He would like to stop taking his metformin and just continue the selenium. He asks you for your opinion.

Selenium is an essential trace mineral that functions as a cofactor for the antioxidant enzymes. Data do not support the use of selenium for the treatment of T2DM, and it has been implicated as a possible risk factor for the development of T2DM.

### Zinc

Zinc is a trace mineral essential for the functioning of cellular processes, including enzymatic processes. Patients with diabetes may be zinc deficient. Evidence exists that zinc may increase glucose transport into cells and thus assist with insulin-induced glucose transport.

**Safety:** Zinc is likely safe when consumed at levels commonly found in food or at levels lower than the tolerable upper level: 4 mg for infants aged 0–6 months, 5 mg for infants aged 7–12 months, 7 mg for children aged 1–3 years, 12 mg for children aged 4–8 years, 23 mg for children aged 9–13 years, 34 mg for children aged 14–18 years, and 40 mg for adults aged 19 years or older.

The most common adverse effects of zinc reported to the California Poison Control System include nausea and vomiting. Caution should be used when zinc is administered as a supplement to patients with gastrointestinal disorders, neurological disorders, hematological disorders, renal insufficiency, immunosuppression, and coagulation disorders, and to men at risk for prostate cancer.

**Known drug interactions:** Possible drug interactions include fluoroquinolones, tetracyclines, and calcium salts.

**Efficacy:** Zinc supplementation in patients with T2DM has been shown to decrease fasting and postprandial blood glucose.

Gupta et al. conducted a double-blind randomized trial assessing the efficacy of zinc supplementation in 50 patients, including healthy controls and those with poorly controlled T2DM and diabetic neuropathy. Each day, participants received 660 mg of zinc sulfate orally. After 6 weeks of treatment, the group receiving zinc plus an oral antidiabetic experienced a significant decrease in fasting blood glucose and preprandial blood glucose compared with before treatment. Significant changes in motor nerve conduction velocity of the median nerve and the common peroneal nerve were also noted. Randomization, power calculations, adverse events, and interactions were not discussed in the study manuscript.

Zinc’s potential benefits cannot be determined based on the available literature. Additional research is required to assess its effect on T2DM prior to making any recommendations to patients.

### Pharmacist-directed practical advice

Some of the most widely used agents in traditional medicine have derived from plant sources, including aspirin, antimalarials, anticancers, and digitalis. However, a current lack of scientific and clinical data establishing the safety and efficacy of many currently available “natural” products hinders their use for medicinal purposes in the general population.

According to ADA, “there is limited evidence that the use of vitamin, mineral, or herbal supplements is necessary in the management of diabetes.” Therefore, ADA does not provide specific recommendations on the use of herbs and dietary supplements for glycemic control.

Of the natural products and dietary supplements discussed, alpha-lipoic acid and fenugreek demonstrate the strongest scientific evidence for lowering blood glucose levels. Additionally, good scientific evidence exists for use of gymnema, vitamin E, and ivy gourd.

Table 1 provides a summary and pocket guide for natural products commonly used in the management of T2DM. Patients should be aware that these products may contain contaminants or inappropriate amounts of active ingredients, as they are not required to undergo the same approval process required for medications in the United States.

Common dietary food sources designated by FDA as “generally recognized as safe” (e.g., cinnamon, dandelion, and onion) can be safely recommended for use in the general diet, with the potential benefit of lowering glucose with minimal adverse effects.

While some assume that consumers use complementary and alternative medicine because of their dissatisfaction with conventional treatment options, a 2004 U.S. study suggests otherwise. Study participants said they were more concerned with the inability of health care providers to understand the use of such products in the medical management of disease states than they were about providers’ potential disapproval. This finding underscores the importance of pharmacists being knowledgeable about the available literature on safety and efficacy of herbal and dietary supplement products, as well as the interaction of these products with other pharmacologic treatments.

Before recommending herbal or dietary supplementation for patients with diabetes, consideration should be given to

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**Table 1: Summary of Natural Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Use for Glycemic Control</th>
<th>Cautions/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gymnema</td>
<td>Helps lower blood glucose</td>
<td>Requires research into safety and efficacy in T2DM</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Helps lower blood glucose</td>
<td>Safety concerns; potential interactions with conventional treatment options</td>
</tr>
<tr>
<td>Ivy gourd</td>
<td>Helps lower blood glucose</td>
<td>Consider potential contamination or inappropriate amounts of active ingredients</td>
</tr>
<tr>
<td>Alpha-lipoic acid</td>
<td>Helps lower blood glucose</td>
<td>Requires further research into safety and efficacy in T2DM</td>
</tr>
</tbody>
</table>

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### Table 1. Pocket guide for commonly used natural products in the management of type 2 diabetes mellitus5,16

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Natural Standard evidence grade for T2DM</th>
<th>Bottom line/counseling points</th>
<th>Commonly studied doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-lipoic acid</td>
<td>A</td>
<td>Alpha-lipoic acid is generally well tolerated when doses do not exceed 1200–1800 mg. Evidence exists that it may aid in the treatment of T2DM and peripheral neuropathy.</td>
<td>300–1800 mg/d</td>
</tr>
<tr>
<td>Alpha-tocopherol/vitamin E</td>
<td>B</td>
<td>Caution is warranted prior to recommending vitamin E supplementation because of a possible increased risk of death from all causes in patients who take high doses.</td>
<td>400–600 IU/d</td>
</tr>
<tr>
<td>Bitter melon</td>
<td>C</td>
<td>Bitter melon has been studied in humans as an oral and subcutaneous agent; however, safety and efficacy data are not readily available for specific doses. Use cautiously in women of child-bearing age (risk of miscarriage). Also avoid use in nursing women, children, patients with gourd/melon allergies, and those with G6PDH deficiency.</td>
<td>2–3 g/d</td>
</tr>
<tr>
<td>Burdock</td>
<td>C</td>
<td>Given the potential of harvesters to confuse burdock with belladonna alkaloids, purity of burdock preparations cannot be guaranteed; contaminated burdock may produce atropine-like effects. Because of safety concerns and lack of efficacy data, burdock should not be recommended at this time. Avoid use in patients with allergies to ragweed, chrysanthemums, marigolds, daisies, or pectin. Use caution when taken with anticoagulants and antiplatelet agents.</td>
<td>90 g/d</td>
</tr>
<tr>
<td>Chromium</td>
<td>C</td>
<td>Chromium is likely safe when used appropriately. Beneficial effects on glucose in patients with T2DM have been documented; however, the results are inconsistent. Additional research is required before recommending to patients for glycemic control. Administration of H₂ blockers may inhibit absorption of chromium. Additionally, coadministration of levothyroxine and chromium should be separated by several hours.</td>
<td>200, 600 mcg/d; 500–1000 mcg/d (picolinate)</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>C</td>
<td>When consumed as a spice for food, cinnamon is likely safe and may lower blood glucose values in patients with diabetes. One gram of cinnamon is equal to approximately one-half teaspoonful per day. It should be noted, however, that cinnamon is a high-risk allergen. Also, avoid concomitant use with anticoagulants.</td>
<td>1–3 g/d</td>
</tr>
<tr>
<td>Dandelion</td>
<td>C</td>
<td>Dandelion is likely safe when used as naturally found in food products. However, human efficacy data for glycemic-lowering effects is severely lacking.</td>
<td>No human data available</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>A</td>
<td>Fenugreek seed powder has more available positive evidence than other herbal supplements for reducing blood glucose levels in patients with T2DM. Gastrointestinal effects may be experienced with its use. Space other oral medications apart from fenugreek administration by at least 2 hours.</td>
<td>5–100 g/d (seed powder)</td>
</tr>
<tr>
<td>Ginseng</td>
<td>C</td>
<td>Asian or American ginseng products may have efficacy as glucose-lowering agents; however, the inability to reliably reproduce efficacy results in trials limits the confident recommendation of these agents for glycemic control.</td>
<td>3, 6 g/d, divided into pre-meal doses</td>
</tr>
<tr>
<td>Gymnema</td>
<td>B</td>
<td>It may be safe to recommend gymnema for glycemic lowering in patients with T2DM, but further well-controlled trials need to be conducted. Counsel patients on the potential for enhanced perception of bitter taste.</td>
<td>400 mg/d</td>
</tr>
<tr>
<td>Nopal</td>
<td>C</td>
<td>Nopal is likely safe when consumed as part of a regular diet and may reduce blood glucose and cholesterol levels. Use with caution in patients taking anticoagulants, antiplatelet agents, or agents metabolized through the CYP450 system.</td>
<td>100–600 g/d</td>
</tr>
<tr>
<td>Onion</td>
<td>C</td>
<td>Onion is likely safe when consumed as a part of regular dietary intake. Caution should be exercised when combined with anticoagulants, antiplatelet agents, blood pressure lowering agents, or agents metabolized through the CYP450 system.</td>
<td>20 g fresh onion consumed three times daily; 25, 50, 100, and 200 g aqueous onion extract</td>
</tr>
<tr>
<td>Psyllium</td>
<td>C (hyperglycemia)</td>
<td>When added to one's regular diet or used as fiber supplementation, psyllium may benefit glycemic control. Oral medications should be taken 1 hour before or 2 hours after psyllium. Additionally, products containing psyllium should be consumed with adequate amounts of water.</td>
<td>5.2 g seed husk two times daily</td>
</tr>
</tbody>
</table>
the type and severity of disease, as well as other agents used for glycemic control. Patients should also be closely monitored for adverse events. Optimal doses of natural products are often unclear, many products are not standardized, and extensive variability can be seen from manufacturer to manufacturer or batch to batch.

Pharmacists must be able to determine which brands of herbal and dietary supplements can be reliably recommended to consumers and use manufacturer labeling as a dosing guide (Table 2). Pharmacists should look for products with recognized symbols of quality (e.g., United States Pharmacopeia and the National Formulary, TruLabel, Consumer Lab) and avoid recommending foreign products unless the quality is known.

### Conclusion

More than 400 herbal agents have been identified for their potential antihyperglycemic effects. However, there is no conclusive evidence that these agents are safer or more effective than other agents currently used in modern medical practice. Pharmacists should encourage patients to seek advice about the addition of these agents for the management of diabetes and consider these agents as adjuncts to pharmacologic treatment. Though limited data are available for the use of herbs and dietary supplements for diabetes care, health care consumers continue to turn to these agents as a means of supplementation and/or management of their disease state. It is essential that pharmacists recognize safety and efficacy issues prior to recommending herbs and dietary supplements for diabetes care.

### References


### Table 1 continued from page 67

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Status</th>
<th>Potential Antihyperglycemic Effects</th>
<th>Categorical Status</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium (prevention)</td>
<td>D</td>
<td>Selenium should be avoided in patients on hemodialysis or immunosuppressants, as well as in those with hyperlipidemia or hypothyroidism. Selenium may increase risk for the development of T2DM.</td>
<td>&lt;800 mcg/d recommended</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>C</td>
<td>Limited data is available on the efficacy of zinc in patients with T2DM. Zinc should not be coadministered with fluoroquinolones, tetracyclines, or calcium salts.</td>
<td>600–660 mg/d</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: CYP450, cytochrome P450; G6PDH, glucose-6-phosphate dehydrogenase; T2DM, type 2 diabetes mellitus.

*Natural Standard evidence-based grading scale key: A, strong scientific evidence; B, good scientific evidence; C, unclear or conflicting scientific evidence; D, fair negative scientific evidence; F, strong negative scientific evidence.*


CPE Assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which botanical agent is a known abortifacient?
   a. Burdock
   b. Bitter melon
   c. Fenugreek
   d. Gymnema

2. Due to theoretical concerns, dandelion use should be avoided in patients with:
   a. Gastric ulcers
   b. Pancreatitis
   c. Anemia
   d. Liver disease

3. An important counseling point for consumers wishing to purchase gymnema would be:
   a. Significant potential for weight gain
   b. Enhanced perception of bitter taste
   c. Avoid combination with anticoagulants
   d. Take 40 minutes prior to meals

4. Based on available data, which agent has good scientific evidence for glucose-lowering efficacy?
   a. Gymnema
   b. Onion
   c. Cinnamon
   d. Nopal

5. Which herbal agent is more likely to increase bleeding risk when used concomitantly with anticoagulants?
   a. Bitter melon
   b. Burdock
   c. Cinnamon
   d. Fenugreek

6. Which agent has a more notable drug–drug interaction with dandelion?
   a. Calcium carbonate
   b. Furosemide
   c. Ciprofloxacin
   d. Orlistat

7. A female with T2DM asks for an herbal supplement to use as an adjunct to her metformin therapy for glycemic control. She takes no other medications and has no other disease states at this time. Based on the available safety and efficacy data, which herbal supplement would be the most appropriate to recommend?
   a. Burdock
   b. Dandelion
   c. Fenugreek
   d. Ivy gourd

8. Which statement is true regarding ginseng?
   a. Siberian ginseng is an acceptable alternative to Panax ginseng.
   b. Studies have demonstrated efficacy when given 40 minutes after meals.
   c. Products are standardized according to the ginsenosides and their ratios.
   d. Doses of 1–9 grams have reduced blood glucose values acutely and long term.

9. Which agent has demonstrated hypoglycemic effects comparable to tolbutamide when given as a single oral dose?
   a. Dandelion
   b. Onion
   c. Cinnamon
   d. Psyllium

10. Which agent should be cautiously recommended in persons with cardiovascular disease because of the potential for contamination during harvesting?
    a. Bitter melon
    b. Burdock
    c. Fenugreek
    d. Dandelion

CPE Information

To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the assessment and evaluation. CPE credit will be awarded for a passing grade of 70% or better on the assessment. You will have two opportunities to successfully complete the CPE assessment. Pharmacists who successfully complete this activity before August 1, 2017, can receive CPE credit. CPE credit is achieved upon successful completion of the assessment and evaluation. Your transcript will be stored on CPE Monitor. Please visit CPE Monitor for your transcript at www.nabp.net/programs/cpe-monitor/cpe-monitor-service.

CPE instructions:
1. Log in or create an account at pharmacist.com and select LEARN from the top of the page; select Continuing Education, then Home Study CPE to access the Library.
2. Enter the title of this article or the ACPE number to search for the article and click on the title of the article to start the home study.
3. To receive CPE credit, select Enroll Now from the left navigation and successfully complete the assessment (with randomized questions) and evaluation.
4. To obtain your CPE credit, click “Claim” on the right side of the page. You will need to provide your NABP e-profile ID number to obtain your CPE credit. Your CPE transcripts will be stored on CPE Monitor. Live step-by-step assistance is available Monday through Friday, 8:30 am to 5:00 pm ET from APhA Member Services at 800-237-APhA (2742) or by e-mailing education@aphanet.com.
11. A reliable brand of herbal supplements to recommend will contain:
   a. Manufacturer’s phone number
   b. Notice of FDA approval
   c. Treatment statement for condition
   d. Recognized symbol of quality

12. Which dietary supplement has data that demonstrate a possible benefit in A1C reduction in patients with T2DM?
   a. Chromium
   b. Pyridoxine
   c. Selenium
   d. Zinc

13. Which fat-soluble vitamin has evidence suggesting that use of high doses may increase the risk of death and, thus, should not be recommended for management of T2DM?
   a. Pyridoxine
   b. Alpha-tocopherol
   c. Alpha-lipoic acid
   d. Zinc

14. Which should be avoided in patients being treated for Parkinson disease?
   a. Selenium
   b. Chromium
   c. Alpha-lipoic acid
   d. Pyridoxine

15. A patient (JM) approaches your community pharmacy counter to ask about appropriate administration of chromium. She would like to try supplemental chromium to aid in glycemic control of her T2DM. You inform her that additional research is needed before you can recommend chromium for glycemic control, but she would still like to try the supplement. JM also has hypothyroidism and frequent heartburn. Which counseling point would you provide JM?
   a. Use of levothyroxine and chromium should be separated by several hours.
   b. Chromium should be administered at the same time as JM’s ranitidine for maximum absorption.
   c. Chromium is contraindicated in patients with hypothyroidism.
   d. Chromium is contraindicated in patients taking metformin.

16. A 62-year-old male patient started alpha-lipoic acid 300 mg daily and pyridoxine 800 mg daily for treatment of his T2DM approximately 8 months ago. He also takes metformin 1500 mg daily. His blood sugar seems to be well controlled at this time. However, he is complaining of peripheral neuropathy pain today. He would like to know what could be causing this new symptom. Which is the most appropriate answer?
   a. Alpha-lipoic acid has been proven to effectively treat neuropathy; thus, he should continue all of his current therapies at the current dose.
   b. Higher doses (>200 mg) of pyridoxine have been associated with reversible neuropathy. He should discontinue the pyridoxine and see his primary care provider.
   c. Higher doses (>200 mg) of alpha-lipoic acid have been associated with reversible neuropathy. He should discontinue the alpha-lipoic acid and see his primary care provider.
   d. Peripheral neuropathy is a complication of T2DM. None of his current therapies have any effect on symptoms of neuropathy.

17. A patient at your pharmacy would like to start taking selenium to help prevent T2DM. Her mother and two of her siblings have T2DM, and she is very concerned about her risk for the disease. She currently has hypertension and hyperlipidemia. What would you recommend for this patient?
   a. She should start selenium immediately to help prevent T2DM and to aid in treatment of her hyperlipidemia.
   b. Prior to starting selenium therapy, she should have the concentration of selenium in her toenails determined. If her concentration is high, she should start selenium supplementation.
   c. She should not take selenium as a supplemental therapy. Data demonstrate an increased risk for the development of T2DM in patients taking selenium. Additionally, selenium should be avoided in patients with hyperlipidemia.
   d. She should not take selenium for prevention of T2DM; however, if she is diagnosed with T2DM, she should begin selenium supplementation to aid in glycemic control.

18. Which supplement has been implicated as a risk factor for the development of insulin autoimmune syndrome?
   a. Alpha-lipoic acid
   b. Chromium
   c. Onion
   d. Pyridoxine

19. Which statement regarding vitamin E is false?
   a. Caution is warranted with the use of high-dose vitamin E because of a possible increased risk of death from all causes.
   b. Vitamin E should be avoided in patients taking anticoagulants.
   c. Vitamin E has been shown to significantly reduce A1C levels in patients with T2DM in randomized, placebo-controlled clinical trials.
   d. Vitamin E should be avoided in patients taking cyclosporine.

20. Which adverse event is frequently reported with the use of supplemental zinc?
   a. Nausea
   b. Encephalitis
   c. Hemorrhage
   d. Congenital heart defects