

# Dietary Supplements for Diabetes Are Decidedly Popular: Help Your Patients Decide

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According to the National Health and Nutrition Examination Study 2003–2006, about half of all Americans use supplements, spending \$14.8 billion annually.<sup>1,2</sup> Various reports describe supplement use by people with diabetes. The National Health Interview Survey reported that 22% of diabetes patients use herbal products.<sup>3</sup> A survey of adult patients with diabetes found that 67% were using some type of vitamin or supplement.<sup>4</sup> Another survey of parents of children with type 1 diabetes found that different modalities and supplements were being used, including aloe vera and cinnamon.<sup>5</sup> Ethnic group differences may partially determine the use of supplements. For example, many Hispanics use herbs such as nopal or aloe vera, and Asians may use other products.<sup>6</sup> A review of medication histories of 459 individuals with diabetes indicated that 55% use a supplement on a daily basis.<sup>7</sup>

Although there may be many explanations for why patients with diabetes take supplements, increased costs of medications and provider visits is one likely reason that individuals may seek more easily accessible supplement products.<sup>7</sup> Other factors may also influence supplement use, including a desire to avoid adverse effects of traditional medications, the belief that supplements are “natural,” the realization that traditional treatments are unable to “cure” diseases, and the powerful suggestions of friends, family members, or coworkers.<sup>8</sup> Diabetes severity and duration may also influence supplement use.<sup>9</sup>

Dietary supplements are used to lower glucose or to treat comor-

bidities such as hypertension and hyperlipidemia. Numerous supplements have been used for diabetes.<sup>10</sup> Widely used and much discussed in the literature are products such as aloe vera, bitter melon, chromium, gymnema sylvestre, fenugreek, ginseng, and nopal. More recently, information has emerged about the use of cinnamon and coenzyme Q10, as well as less well-known but increasingly popular products, including benfotiamine, berberine, hibiscus, mulberry, turmeric, and vinegar.

Diabetes clinicians should become familiar with these products and provide evidence-based information to their patients, but they must also caution patients that long-term safety information is not available. More than half of Class 1 drug recalls in the United States involve supplements. Class 1 recalls are for products for which there is a reasonable probability that use may result in serious adverse health outcomes or possibly death.<sup>11</sup> A report on vitamins and supplements in the September 2012 issue of *Consumer Reports* stated that > 6,300 serious adverse events involving supplements were reported to the U.S. Food and Drug Administration (FDA) between 2007 and 2012; these reports involved emergency room visits, hospitalizations, and 115 deaths.<sup>12</sup>

## **Benfotiamine (Other Names: Vitamin B1, Allithiamines)**

People with neuropathy may have a thiamine deficiency.<sup>13</sup> Different neurological disorders, including diabetes and alcohol-related neuropathy, have been treated with vitamin B1 (thiamine).

Although B1 is sold as a supplement, clinicians are reminded that it is an important vitamin. However, thiamine is not well absorbed, and high doses are needed for successful treatment. Benfotiamine, a fat-soluble form of thiamine, provides much higher blood and tissue levels and thus may be a more effective form.<sup>14</sup> Benfotiamine is also manufactured in combination with other B vitamins as well as alpha lipoic acid. Another name for this group of vitamins is allithiamines because they are found in the *Allium* vegetable family, including garlic and onions.<sup>14</sup> Benfotiamine has been used for diabetes-related neuropathy in both type 1 and type 2 diabetes.

Some studies of benfotiamine have had an open-label design, whereas others were randomized controlled trials (RCTs). One open-label, 6-week study in 36 patients with type 1 or type 2 diabetes looked at different doses of benfotiamine in combination with B vitamins. Although all groups had beneficial effects, the best results were reported in patients taking the highest dose ( $P < 0.01$  for all parameters compared to baseline).<sup>15</sup> Another open-label, 3-month study in 45 people with type 1 or type 2 diabetes compared benfotiamine (combined with other B vitamins) to a conventional B vitamin control group. Although improvement occurred in both groups, the benfotiamine group had significant neuropathic pain relief ( $P < 0.001$ ) and an improved vibration perception threshold.<sup>16</sup> A short, 3-week randomized trial reported improved neuropathy symptoms ( $P < 0.05$ ) in 40 patients with type 1 or type 2 diabetes.<sup>17</sup> A randomized, 6-week study in 133 patients with type 1 or type 2 diabetes compared two doses of benfotiamine to placebo. The neuropathy symptom score was significant in the per protocol population ( $P = 0.033$ ) but not in the intention-to-treat population.<sup>18</sup> A randomized, 12-week study in 24 patients with type 1 or type 2 diabetes comparing a benfotiamine plus a vitamin B6 and B12 combination to placebo used higher benfotiamine doses for 2 weeks and

then a lower dose for 10 weeks. The benfotiamine group had improved vibration perception threshold scores in the metacarpal and metatarsal nerves, although the results were not significant. The benfotiamine group also had improved nerve conduction velocity in the peroneal nerve ( $P = 0.006$ ) but not the median nerve.<sup>19</sup>

Study results are not always positive. A 24-month, randomized trial in 67 patients with type 1 diabetes found no benefit with benfotiamine for peripheral nerve function.<sup>20</sup> However, the results of this study have been questioned by other researchers.<sup>21</sup>

Although benfotiamine has been highly studied for neuropathy, it has also been studied for retinopathy<sup>22</sup> and nephropathy.<sup>23,24</sup> There have been numerous studies with varying results, and study designs were not always optimal.

Benfotiamine enhances transketolase activity (the rate-limiting enzyme of the pentose phosphate pathway) and thus may inhibit three major pathways possibly involved in vascular damage (the diacylglycerol-protein kinase C pathway, the advanced glycation end product formation pathway, and the hexosamine pathway).<sup>14,22</sup> Transketolase activation also blocks hyperglycemia-induced activation of nuclear factor  $\kappa$ B, a pro-inflammatory transcription factor.<sup>22</sup> It may also diminish or correct cell damage by normalizing cell division rates and decreasing apoptosis.<sup>14</sup>

There are no reports of major side effects, but people who are prone to allergy may experience skin rashes.<sup>14</sup> Certain botanical dietary supplements may decrease thiamine activity, such as betel nuts (*Areca*), and others, such as horsetail (*Equisetum*), may cause thiamine deficiency.<sup>13</sup> Antibiotics, oral contraceptives, diuretics, some seizure medications, and chemotherapeutic agents may decrease the body's natural thiamine levels.<sup>13</sup> Interestingly, metformin may also decrease thiamine activity. The doses that have been studied in people with diabetes are 300–600 mg/day, administered

in divided doses (e.g., 100 or 150 mg taken three times daily).<sup>15–19</sup>

### **Berberine (*Coptis chinensis* [*Huanglian* or *French*])**

Berberine is an isosquinoline plant alkaloid that is extracted from many different plants, including the Chinese herb *Coptis chinensis* (*Huanglian* or *French*), goldenseal, European barberry, tree tumeric, and others. It has been found to lower glucose when used to treat bacterial diarrhea in people with diabetes.<sup>25</sup> It also has lipid-lowering and weight loss effects.<sup>26</sup>

Berberine was compared to placebo in a 3-month study in 116 people with newly diagnosed type 2 diabetes and hyperlipidemia.<sup>26</sup> Subjects took 500 mg twice daily or a placebo, and there was a significant decrease in A1C and fasting and postprandial glucose in the berberine group compared to placebo ( $P < 0.0001$  for each parameter). A1C decreased from 7.5 to 6.6% in the berberine group and from 7.6 to 7.3% in the placebo group. There were also significant decreases favoring berberine in LDL cholesterol ( $P < 0.0001$ ), weight ( $P = 0.034$ ), and systolic blood pressure ( $P = 0.038$ ).

Another RCT evaluated two groups with type 2 diabetes, one newly diagnosed and the other poorly controlled.<sup>27</sup> The newly diagnosed group took berberine or metformin for 3 months. In both newly diagnosed groups, there were significant declines from baseline in A1C, fasting glucose, and postprandial glucose ( $P < 0.01$  compared to baseline). A1C decreased from 9.5 to 7.5% in the berberine group and from 9.2 to 7.7% in the metformin group. Fasting glucose decreased from 191 to 123 mg/dl in the berberine group and from 179 to 129 mg/dl in the metformin group. Postprandial glucose decreased from 357 to 199 mg/dl in the berberine group and from 370 to 232 mg/dl in the metformin group. The authors did not provide a statistical analysis of the comparison between berberine and metformin, but the numbers were very similar. Patients in the poorly controlled group continued their medications (oral hypoglycemic

agents or insulin), adding berberine for 3 months. A1C decreased from 8.1 to 7.3%, fasting glucose decreased from 173 to 137 mg/dl, and postprandial glucose decreased from 266 to 194 mg/dl. Decreases were all statistically significant ( $P < 0.001$  for all three parameters).

A different randomized study evaluated 97 type 2 diabetes patients for 2 months.<sup>28</sup> Of these, 50 were randomized to berberine, 26 to metformin, and 21 to rosiglitazone. Fasting glucose and A1C decreased significantly from baseline in all three groups ( $P < 0.001$  for berberine and metformin,  $P < 0.01$  for rosiglitazone). A1C decreased from 8.3 to 6.8% in the berberine group, from 9.4 to 7.2% in the metformin group, and from 8.3 to 6.8% in the rosiglitazone group. Triglycerides decreased significantly only in the berberine group ( $P < 0.01$ ).

There are a variety of theorized mechanisms for the therapeutic effects of berberine. It may enhance glucose-stimulated insulin secretion, facilitate glucose transporter type 4 translocation, exert  $\alpha$ -glucosidase inhibitor activity, enhance adenosine monophosphate-activated protein-kinase, increase insulin receptor expression, and possibly upregulate LDL receptors.<sup>26,28</sup>

The main side effects of berberine are abdominal upset and constipation.<sup>25</sup> However, it should not be used by pregnant or lactating women or in infants because it may result in fatal kernicterus.<sup>13</sup> Berberine may inhibit certain cytochrome P 450 enzymes (CYP3A4) and thus increase levels of cyclosporine or other drugs metabolized by this system (i.e., certain statins and some calcium channel blockers).<sup>13</sup> It may also be involved in CYP2D6 metabolism.<sup>29</sup> Thus, caution is warranted when it is used with other agents.

Berberine was evaluated in a meta-analysis of 14 RCTs involving 1,068 subjects and found to be significantly more effective than placebo and as effective as metformin, sulfonylureas, or glitazones. It was also effective when combined with glucose-lowering agents.<sup>25</sup> Doses studied have been 500 mg two or three times daily.

### Cinnamon (*Cinnamomum cassia*)

Cinnamon is a widely used supplement for diabetes and hyperlipidemia. There have been several studies of cinnamon with varying results. A meta-analysis of five clinical trials involving 282 people with diabetes indicated that doses of 1–6 g/day of cassia cinnamon resulted in decreased fasting glucose and lipids but not A1C.<sup>30</sup> A real-world, 3-month study in 102 people with type 2 diabetes found a significant decrease in A1C of 0.83% using 1 g/day.<sup>31</sup> Another smaller study in 58 people with type 2 diabetes showed a small decrease in A1C of only 0.36% with 2 g/day.<sup>32</sup> A Cochrane Database systematic review evaluating 10 RCTs of 577 people concluded that there is insufficient evidence to support cinnamon use.<sup>33</sup> A different meta-analysis of six clinical trials involving 435 people found that cinnamon improved fasting glucose by 15 mg/dl and only slightly decreased A1C in short-term studies.<sup>34</sup>

There is much controversy regarding the appropriate form of cinnamon, but most studies have used cassia cinnamon. The main active ingredients are procyanidin type-A polymers.<sup>35</sup> Various theorized mechanisms include enhanced insulin action, increased phosphorylation of the insulin receptor, and overall facilitation of the insulin signaling system,<sup>13,35–37</sup> as well as possible  $\alpha$ -glucosidase inhibitor activity<sup>38</sup> and possible activation of peroxisome proliferator-activated receptors.<sup>39</sup> Cinnamon also decreases postprandial glucose.<sup>40</sup>

Side effects include topical allergic reactions and possible bleeding or hepatotoxicity because of cinnamon's coumarin content.<sup>13,36</sup> Interactions would include possible hypoglycemia if combined with secretagogues or bleeding if combined with any agent (supplement or medication) that may have anticoagulant properties.<sup>13,36</sup>

The most appropriate form of cinnamon is unknown, and it remains controversial whether supplements should be the whole powdered spice (possibly a combination of different types of cinnamon) or an aqueous extract.<sup>39</sup> Doses have ranged from 1 to 6 g/day. Overall, cinnamon

continues to be widely used and may have more benefits than drawbacks.

### Coenzyme Q10 (Ubiquinone)

Coenzyme Q10 (CoQ10) is one of the most frequently used supplements in people both with and without diabetes. CoQ10 is a vitamin-like substance that is thought to be deficient in many diseases, including diabetes.<sup>41,42</sup>

It has been used for a variety of cardiovascular diseases, including hypertension, angina, heart failure, and statin-induced myopathy, as well as other disease states, including Parkinson's disease.<sup>41,43,44</sup> A recent meta-analysis of CoQ10 in heart failure showed improved ejection fraction and a slight improvement in New York Heart Association functional class. However, the analysis included few studies, and many were older evaluations in which patients were not taking agents that are now commonly used to treat heart failure.<sup>45</sup> In combination with selenium, CoQ10 has been shown to decrease biomarkers associated with adverse outcomes and decreased cardiovascular mortality.<sup>46</sup>

In 34 patients with type 1 diabetes, CoQ10 resulted in a non-significant decline in fasting glucose (from 160 to 145 mg/dl) and A1C (from 8.04 to 7.86%).<sup>47</sup> It has been shown to have a statistically significant benefit in glucose control and blood pressure in 74 patients with type 2 diabetes when combined with fenofibrate (A1C decreased significantly from 7.5 to 7.2%; systolic pressure decreased by 6.1 mmHg; and diastolic pressure decreased by 2.9 mmHg).<sup>48</sup> Another small study in nine type 2 diabetes patients showed that CoQ10 decreased A1C from 7.1 to 6.8% ( $P = 0.03$ ).<sup>49</sup>

Recent study has indicated that CoQ10 supplementation may attenuate hyperglycemia due to reduced glucose transporter type 4 protein levels caused by some statins.<sup>50</sup> One of the main reasons it is used in diabetes is that it reduces endothelial dysfunction.<sup>51</sup>

CoQ10 is produced endogenously. Also known as ubiquinone, it has a 10-carbon side chain and is similar in structure to vitamin K.<sup>13,41</sup> It is an antioxidant that may increase

adenosine triphosphate production, scavenge oxygen free radicals, and stabilize membranes.<sup>13,41,43</sup>

CoQ10 does not exhibit serious effects in long-term trials. The most serious drug interaction may occur in patients taking warfarin because CoQ10 may decrease the International Normalized Ratio due to its structural similarity to vitamin K.<sup>13,41</sup> It may also decrease adriamycin-induced cardiotoxicity and potentially produce additive blood pressure-lowering effects with antihypertensives or additive hypoglycemia with secretagogues.<sup>13,41</sup> Overall, doses have ranged from 100 to 600 mg/day.

Although the exact role of CoQ10 in diabetes is unknown, it may benefit the cardiovascular risk factors that plague patients with diabetes. Fortunately, it has demonstrated long-term safety.

### Hibiscus (*Hibiscus sabdariffa* L.)

Hibiscus is a shrub that bears brightly colored flowers. In patients with or without diabetes, its bloom is used to make tea as a treatment for hypertension and hyperlipidemia. This product is known by a variety of names, including “hibiscus tea,” “roselle,” “agua de Jamaica,” “sour tea,” and others.<sup>52</sup>

Hibiscus flowers and tea sachets steeped in water have shown blood pressure-lowering effects. In comparison to ACE inhibitors, hibiscus was as effective as captopril, but less effective than lisinopril in lowering blood pressure.<sup>53,54</sup> In a 4-week comparison of hibiscus tea and black tea, 27 people with type 2 diabetes and hypertension who took hibiscus experienced a significant decrease in blood pressure (from 134.4 to 112.7 mmHg), whereas 26 in the comparison group had an increase in blood pressure (from 118.6 to 127.3 mmHg) ( $P < 0.001$  for hibiscus versus black tea).<sup>55</sup> In the same 27 people with type 2 diabetes, LDL cholesterol decreased from 137.5 to 128.5 mg/dl, whereas the 26 in the comparison group had an increase in LDL ( $P < 0.003$  for hibiscus vs. black tea).<sup>56</sup>

Two reviews of hibiscus have concluded that evidence favoring its

use is inconclusive and recommended more study.<sup>54,57</sup>

The active chemical constituents of hibiscus include anthocyanins (including delphinidin-3-sambubioside and cyanidin-3-sambubioside)<sup>52</sup> and polyphenols<sup>53</sup> that may exert the antihypertensive effects through ACE inhibition and vasorelaxation,<sup>52</sup> as well as through diuretic properties. Lipid-lowering effects are attributed to the polyphenol content and may be the result of inhibition of LDL cholesterol oxidation.<sup>53</sup> Possible drug interactions include decreased elimination half-life of diclofenac,<sup>58</sup> increased retention of hydrochlorothiazide when co-administered,<sup>59</sup> and enhanced acetaminophen elimination.<sup>60</sup>

Hibiscus is used as a tea, and there are no standardized doses. Steeping the flowers in boiling water has been described,<sup>53</sup> but there are also commercially available tea bags or sachets that are steeped in water for a few minutes.<sup>13</sup>

Overall, the benefits are mainly for mild hypertension, shown in trials that were small in number of patients, of short duration, and suboptimal in study design. However, better designed trials are emerging,<sup>52</sup> and the glucose-lowering effects of hibiscus are being studied.<sup>61</sup>

When patients report that they use “teas” to treat their diseases, clinicians should ask patients about the specific teas or other products they use because hibiscus may be among them. Hispanic patients often report “agua de Jamaica” as a commonly used beverage, and they may not recognize the term “hibiscus.”

### Mulberry (*Morus alba*)

Mulberry leaf tea and extract have been widely used in Asia for diabetes. A 30-day study in 24 people with type 2 diabetes compared mulberry to a sulfonylurea. Mulberry significantly decreased fasting glucose from 153 to 110 mg/dl ( $P < 0.01$ ), LDL cholesterol from 102 to 79 mg/dl ( $P < 0.01$ ), and triglycerides from 200 to 68 mg/dl ( $P < 0.01$ ) and increased HDL cholesterol from 50 to 59 mg/dl ( $P < 0.01$ ).<sup>62</sup> In another small, 30-day study, mulberry leaf was combined with propolis in 12 people with type 2 diabetes and significantly lowered

blood glucose from 202.8 to 129 mg/dl and A1C from 7.8 to 7%.<sup>63</sup> A different cross-over study compared 10 people with type 2 diabetes to 10 people without diabetes who received 1 g mulberry leaf before a 75-g sucrose challenge to evaluate the attenuation of increase in blood glucose. In both groups, mulberry attenuated the increase in blood glucose, and carbohydrate malabsorption was greater in the mulberry group.<sup>64</sup>

A proprietary mulberry leaf extract is used for diabetes. Mulberry leaf contains various active ingredients, including 1-deoxynojirimycin, fagomine, and antioxidants, and its berries contain resveratrol.<sup>13,65</sup> The ingredient 1-deoxynojirimycin has  $\alpha$ -glucosidase inhibitor activity,<sup>65</sup> fagomine may induce insulin secretion,<sup>66</sup> and the antioxidants may decrease lipid peroxidation.<sup>65</sup>

Theoretical expected side effects would be gastrointestinal upsets similar to  $\alpha$ -glucosidase inhibitors, and theoretical drug interactions may be additive glucose-lowering effects with secretagogues.<sup>13</sup>

Although not well characterized, doses used in studies have ranged from 1 g before an oral glucose tolerance test to 3 g daily. Combinations of black, green, and mulberry tea are also being used.

The overall benefit may be decreased carbohydrate absorption. Thus, mulberry may sometimes be used with a large meal to decrease postprandial glucose levels.

### Turmeric (*Curcuma longa*)

Turmeric is a spice recognized for its anti-inflammatory medicinal properties. Because diabetes is considered an inflammatory disease, it is no surprise that research evaluating turmeric for diabetes and its comorbidities is emerging.<sup>67</sup> Turmeric is a perennial that grows in Southern Asia, and its roots, rhizomes, and bulbs are used. When boiled and dried, these parts turn into a bright yellow powder.<sup>68</sup>

One study evaluated the effect of turmeric on postprandial glucose and insulin levels in people without diabetes who were given a 75-g oral glucose tolerance test. The subjects were given 6 g of *Curcuma longa* or

a placebo, and fingerstick glucose readings and venous samples were obtained every 15 minutes for 120 minutes. The insulin response was higher after 30 minutes ( $P = 0.048$ ) and 60 minutes ( $P = 0.033$ ), but there was no effect on glucose.<sup>69</sup> A recent evaluation determined that turmeric may have benefit in preventing type 2 diabetes. In the 9-month, randomized, double-blind, placebo-controlled trial, 240 patients with prediabetes were given 1,500 mg/day of turmeric or a placebo. At the end of the study, 16.4% of patients on placebo had developed type 2 diabetes, whereas there were no cases in those taking turmeric ( $P < 0.001$ ). Furthermore, turmeric improved  $\beta$ -cell function with higher homeostatic model assessment- $\beta$ , lower C-peptide, and higher adiponectin levels.<sup>70</sup> In 40 type 2 diabetes patients with nephropathy, a 2-month RCT showed that 1,500 mg of turmeric daily improved urinary protein excretion compared to placebo.<sup>71</sup> Turmeric in a lecithinized system was given to 38 people with diabetes for diabetic microangiopathy and retinopathy.<sup>72</sup> Microangiopathy improved, including improved venoarteriolar response and decreased peripheral edema. Retinal edema also improved and was associated with improved visual acuity.

Curcumin, is the principal ingredient in turmeric, and is the major constituent of curry powder. The active ingredient is diferuloylmethane, a hydrophobic polyphenol with a characteristic yellow color.<sup>73</sup> Turmeric exhibits  $\alpha$ -glucosidase inhibitor activity<sup>74</sup> and may also exert other effects through improved  $\beta$ -cell function and decreased insulin resistance.<sup>12</sup> Turmeric has anti-inflammatory effects, inhibits nuclear factor  $\kappa$ B,<sup>75</sup> and may stimulate glucagon-like peptide 1 secretion.<sup>76</sup> Also, because dietary turmeric is poorly absorbed, it is being manufactured in a unique formulation using nanoparticles and lipid/liposome particles to improve absorption and bioavailability.<sup>75</sup>

Side effects are mostly abdominal upset and allergic dermatitis, and turmeric may increase bleeding when co-administered with antiplatelet

agents such as warfarin, clopidogrel, or aspirin.<sup>13</sup> Also, additive hypoglycemia may occur if taken with secretagogues.<sup>13</sup>

Turmeric has garnered interest for its many potential therapeutic benefits for diabetes. Doses used have ranged from 1,500 mg to 6 g daily. Absorption of the active ingredient may be enhanced if it is taken with food. Because of its antiplatelet activity, patients should be counseled to stop using the supplement 2 weeks before surgery to prevent excessive bleeding.<sup>13</sup>

### Vinegar

Many people are interested in adding vinegar to their diet. A small, randomized study of 10 patients with well-controlled type 1 diabetes evaluated the effect of vinegar on postprandial glucose. The study showed that vinegar use significantly decreased postprandial glucose by 20% after a standardized meal ( $P = 0.005$ ).<sup>77</sup> A complicated, randomized, double-blind, crossover study of 38 patients with or without diabetes consisted of four sub-trials.<sup>78</sup> The study found that ~2 tsp of vinegar taken with meals decreased postprandial glucose by about 20%.<sup>78</sup> Another small, randomized trial in 27 patients with type 2 diabetes showed that vinegar resulted in a small decrease in A1C ( $P = 0.018$ ).<sup>79</sup> Yet another small, randomized study in 11 people with well-controlled type 2 diabetes found that vinegar given at bedtime decreased fasting glucose ( $P = 0.033$ ).<sup>80</sup>

Acetic acid is the main active chemical ingredient in vinegar.<sup>79</sup> The mechanism of action of vinegar in diabetes is varied. Vinegar may delay gastric emptying, inhibit disaccharide activity, and promote muscle glucose uptake.<sup>79</sup> It may also alter the glycolysis and hepatic gluconeogenesis cycle, which may benefit individuals who experience the “dawn phenomenon” (an early-morning increase in glucose level).<sup>80</sup>

Most side effects from vinegar are gastrointestinal in nature.<sup>81</sup> However, hypoglycemia has been reported in type 1 diabetes patients with gastroparesis.<sup>82</sup> Oropharyngeal inflammation and caustic esophageal injury have also been reported.<sup>83</sup> A

case report involving ingestion of large amounts of vinegar reported hypokalemia.<sup>84</sup> Drug interactions are mainly theoretical and related to the mechanism of action of vinegar. They could involve additive hypoglycemia with secretagogues or problems when used with agents that pose a hypokalemia risk, such as digoxin.<sup>13,84</sup>

Vinegar has aroused much interest for its potential effects in improving postprandial glucose elevations. Some authors have suggested that as little as 2 tsp of vinegar used in a salad, for example, may attenuate increased postprandial glucose.<sup>78</sup>

### Summary

Many dietary supplements are used for diabetes and its comorbidities.<sup>10,85,86</sup> However, there is no exact information regarding how many people with diabetes use supplements or which supplements are most widely used. Consumer habits vary, and the popularity of various supplements may change over time. Variability in dosage forms and inconsistent information, such as the exact botanical parts that are used, as well as a lack of adequate dose-finding studies may be problematic.

Clinicians must realize that patients believe supplements are “natural,” but may not know that they contain active chemical constituents with pharmacological activity and may cause adverse effects and drug interactions. There are many instances in which adverse events secondary to supplement use have been reported to the FDA and many supplements have been recalled.<sup>11,12</sup> Furthermore, supplements have not been unequivocally found to decrease the morbidity and mortality associated with diabetes or its comorbidities. However, there is a great amount of ongoing research, and it is important for clinicians to be unbiased and stay informed about this subject.

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