Systematic Review of Herbs and Dietary Supplements for Glycemic Control in Diabetes

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OBJECTIVE — To conduct a systematic review of the published literature on the efficacy and safety of herbal therapies and vitamin/mineral supplements for glucose control in patients with diabetes.

RESEARCH DESIGN AND METHODS — We conducted an electronic literature search of MEDLINE, OLDMEDLINE, Cochrane Library Database, and HealthSTAR, from database inception to May 2002, in addition to performing hand searches and consulting with experts in the field. Available clinical studies published in the English language that used human participants and examined glycemic control were included. Data were extracted in a standardized manner, and two independent investigators assessed methodological quality of randomized controlled trials using the Jadad scale.

RESULTS — A total of 108 trials examining 36 herbs (single or in combination) and 9 vitamin/mineral supplements, involving 4,565 patients with diabetes or impaired glucose tolerance, met the inclusion criteria and were analyzed. There were 58 controlled clinical trials involving individuals with diabetes or impaired glucose tolerance (42 randomized and 16 nonrandomized trials). Most studies involved patients with type 2 diabetes. Heterogeneity and the small number of studies per supplement precluded formal meta-analyses. Of these 58 trials, the direction of the evidence for improved glucose control was positive in 76% (44 of 58). Very few adverse effects were reported.

CONCLUSIONS — There is still insufficient evidence to draw definitive conclusions about the efficacy of individual herbs and supplements for diabetes; however, they appear to be generally safe. The available data suggest that several supplements may warrant further study. The best evidence for efficacy from adequately designed randomized controlled trials (RCTs) is available for Gymnema sylvestre and American ginseng. Chromium has been the most widely studied supplement. Other supplements with positive preliminary results include Gymnema sylvestre, Aloe vera, vanadium, Momordica charantia, and nopal.

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Diabetes is a predominant public health concern, affecting ∼16 million persons in the U.S. The disease causes substantial morbidity, mortality, and long-term complications and remains an important risk factor for cardiovascular disease. With increasing rates of childhood and adult obesity, diabetes is likely to become even more prevalent over the coming decade (1).

In response to the increasing use of complementary and alternative medicine (CAM) among the general public (2,3), the American Diabetes Association issued a Position Statement in 2001 on “Unproven Therapies” that encouraged health care providers to ask their patients about alternative therapies and practices, evaluate each therapy’s effectiveness, be cognizant of any potential harm to patients, and acknowledge circumstances in which new and innovative diagnostic or therapeutic measures might be provided to patients (4).

Recently, two national surveys have examined CAM use among those with diabetes. One study, using 1996 Medical Expenditure Panel Survey data, reported that ∼8% of respondents with diabetes saw a CAM professional for care (5). A nationally representative survey conducted in 1997–1998 reported that about one-third of respondents with diabetes use CAM to treat their condition (6). In other surveys of specific diabetic populations, 39% of Navajo, two-thirds of Vietnamese, and 49% of a largely Hispanic population in South Texas used CAM (7–9).

In general, the scientific literature on the efficacy of CAM in the treatment of diabetes is relatively sparse and heterogeneous. Studies have examined mind-body techniques, biofeedback, relaxation, qigong (10–17), massage therapy, yoga, alternative dietary/lifestyle modifications (18), aromatherapy, acupuncture, and other systems of healing such as traditional Chinese medicine (TCM) (19–30).

Most of the literature, however, has focused on herbs or other dietary supplements. This finding parallels results from prevalence surveys that report herbal remedies or other dietary supplements taken by mouth to be consistently among the top CAM therapies used, regardless of the sample surveyed (5,6,8,9,31).

Plant derivatives with purported hypoglycemic properties have been used in folk medicine and traditional healing systems around the world (e.g., Native American Indian, Jewish [32], Chinese [20], East Indian, Mexican). Many modern pharmaceuticals used in conventional
Table 1—Controlled clinical trials of single herbs for glycemic control*

<table>
<thead>
<tr>
<th>Herb/Supplement</th>
<th>Reference</th>
<th>Design</th>
<th>Sample</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Evidence Direction</th>
<th>Jadad</th>
<th>Adverse Effects/Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allium sativum (Garlic)</td>
<td>Sitprija S et al (1987)</td>
<td>Double-blind; 2 parallel groups</td>
<td>33 Type 2; diet alone</td>
<td>Garlic; 700 mg/d (preparation unspecified); for 4 wks</td>
<td>Placebo</td>
<td>No change in FBG, PPG; insulin</td>
<td>-</td>
<td>2</td>
<td>No side effects; no effect on liver function</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Bunyapraphatsara N et al (1996)</td>
<td>Non-randomized; Single-blind; 2 parallel groups</td>
<td>76 Type 2; uncontrolled on OHA</td>
<td>Aloe vera Linn. 80% juice; 1 tbsp BID (prepared by Faculty of Pharmacy, Mahidol University, Thailand); for 42 d</td>
<td>Placebo juice</td>
<td>Decrease FBG</td>
<td>+</td>
<td>N/A</td>
<td>No effects on liver/ kidney function</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Yongchaeyudha S et al (1996)</td>
<td>Non-randomized; Single-blind; 2 parallel groups</td>
<td>40 Type 2; newly diagnosed</td>
<td>Aloe vera Linn. 80% juice; 1 tbsp BID (prepared by Faculty of Pharmacy, Mahidol University, Thailand); for 42 d</td>
<td>Placebo juice</td>
<td>Decrease FBG</td>
<td>+</td>
<td>N/A</td>
<td>1/40 ketosis (group not reported)</td>
</tr>
<tr>
<td>Artocarpus heterophyllus</td>
<td>Fernando MR et al (1991)†</td>
<td>Non-randomized; Open-label; Crossover; Short-term metabolic trial</td>
<td>10 Type 2; no diabetes medication</td>
<td>Artocarpus heterophyllus; 200 mg fresh leaves boiled decoction; single experimental dose prior to GTT</td>
<td>Distilled water</td>
<td>Decrease PPG</td>
<td>+</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>Asteracanthus longifolia</td>
<td>Fernando MR et al (1991)†</td>
<td>Non-randomized; Open-label; Crossover; Short-term metabolic trial</td>
<td>10 Type 2; no diabetes medication</td>
<td>Asteracanthus longifolia; 100 mg fresh leaves boiled decoction; single experimental dose prior to GTT</td>
<td>Distilled water</td>
<td>Decrease PPG</td>
<td>+</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bauhinia forficata</td>
<td>Russo EMK et al (1990)</td>
<td>Double-blind; Crossover</td>
<td>16 Type 2; diet and OHA</td>
<td>Bauhinia forficata tea; 3 g/d (1 g individual tea bags from dried leaves); for 8 wks</td>
<td>Placebo herb tea (sape, Imperata brasiliensis)</td>
<td>No change in FBG, HgbA1C, insulin</td>
<td>-</td>
<td>3</td>
<td>No side effects; no effect on liver/ kidney function</td>
</tr>
<tr>
<td>Cocconia indica</td>
<td>Azad Khan AK et al (1979)</td>
<td>Double-blind; 2 parallel groups</td>
<td>32 Type 2; uncontrolled or untreated</td>
<td>Cocconia indica leaf; 1800 mg/d (freeze-dried powder from fresh leaves in tablets); for 6 wks</td>
<td>Placebo tablet</td>
<td>Decrease FBG, PPG</td>
<td>++</td>
<td>4</td>
<td>No side effects; no effect on liver/ kidney function</td>
</tr>
<tr>
<td>Cocconia indica</td>
<td>Kamble SM et al (1996)</td>
<td>Non-randomized; Open-label; 3 parallel groups</td>
<td>70 Type 2; other medications unclear</td>
<td>Cocconia indica; 6 g/d (dried pellets from fresh leaves); for 12 wks</td>
<td>No treatment, OHA</td>
<td>Decrease FBG, PPG (similar to OHA)</td>
<td>++</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ficus carica (Fig leaf)</td>
<td>Serracakra A et al (1998)</td>
<td>Open-label; Crossover</td>
<td>10 Type 1; diet and insulin</td>
<td>Fig leaf tea; 13 g/d leaf decoction; for 4 wks</td>
<td>Bitter commercial tea blend</td>
<td>Decrease PPG, insulin requirement; no change in PPG, C peptide, HgbA1C</td>
<td>+</td>
<td>2</td>
<td>No side effects</td>
</tr>
<tr>
<td>Ginseng (Unspecified)</td>
<td>Sotaniemi EA et al (1995)</td>
<td>Double-blind; 3 parallel groups</td>
<td>36 Type 2; newly diagnosed; diet alone</td>
<td>Ginseng; 100 mg/d vs. 200 mg/d (tablet preparation Dansk Droge, Copenhagen); for 8 wks</td>
<td>Placebo tablet</td>
<td>Decrease FBG, HgbA1C (200 mg); no change in BG, insulin, C peptide during GTT</td>
<td>+</td>
<td>3</td>
<td>No side effects</td>
</tr>
<tr>
<td>Herb</td>
<td>Authors</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Treatment</td>
<td>Outcome Measures</td>
<td>Comments</td>
<td></td>
<td></td>
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<td>-------------------------------</td>
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<tr>
<td><strong>Ginseng (American)</strong></td>
<td>Vuksan V et al (2000)</td>
<td>Single-blind; Multiple crossover, Short-term metabolic trial</td>
<td>10 Type 2; diet and/or OHA</td>
<td>Ground root of American Ginseng, 3g vs 6g vs 9g capsules (Chai-Na-Ta Corp, British Columbia); single experimental dose at varying times prior to GTT</td>
<td>Identical placebo capsule containing corn flour</td>
<td>Decrease PPG (all doses), no difference between doses or administration times (3)</td>
<td>No side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ginseng (American)</strong></td>
<td>Vuksan V et al (2000)</td>
<td>Single-blind; Multiple crossover, Short-term metabolic trial</td>
<td>9 Type 2; well-controlled on diet and/or OHA</td>
<td>Ground root of American Ginseng, 3g capsule (Chai-Na-Ta Corp, British Columbia); single experimental dose at varying times prior to GTT</td>
<td>Identical placebo capsule containing corn flour</td>
<td>Decrease PPG (given at 0, −40min) (2)</td>
<td>Mild insomnia (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ginseng (American)</strong></td>
<td>Vuksan V et al (2001)</td>
<td>Double-blind; Crossover</td>
<td>24 Type 2; diet and/or OHA</td>
<td>American Ginseng extract, 3g/d (standardized extract, Chai-Na-Ta Corp, British Columbia); for 8 wks</td>
<td>Placebo capsule</td>
<td>Decrease HgbA1C, FBG, no change insulin (++) (2)</td>
<td>No effect on liver/kidney function</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gymnema sylvestre</strong></td>
<td>Baskaran K et al (1990)</td>
<td>Non-randomized; Open-label, 2 parallel groups</td>
<td>47 Type 2; all on OHA</td>
<td>Gymnema sylvestre extract, GS4, 400 mg/d capsule; for 18–20 mos</td>
<td>No GS4 treatment</td>
<td>Decrease FBG, HgbA1C, glycosylated plasma protein, conventional medication, urine glucose; increase insulin (++) (N/A)</td>
<td>Not reported</td>
<td></td>
<td></td>
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<tr>
<td><strong>Gymnema sylvestre</strong></td>
<td>Shanmugasundaram ERB et al (1990)</td>
<td>Non-randomized; Open-label, 2 parallel groups</td>
<td>64 Type 1; all on insulin</td>
<td>Gymnema sylvestre extract, GS4, 400 mg/d capsule; for 2–30 mos</td>
<td>No GS4 treatment</td>
<td>Decrease FBG, HgbA1C, glycosylated plasma protein, insulin requirement, urine glucose; increase C-peptide (++) (N/A)</td>
<td>No side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Momordica charantia</strong></td>
<td>Welhinda J et al (1986)</td>
<td>Non-randomized; Open-label, Crossover, Short-term metabolic trial</td>
<td>18 Type 2; newly diagnosed</td>
<td>Momordica charantia juice; homemade preparation (dose unspecified); single experimental dose prior to GTT</td>
<td>Distilled water</td>
<td>Decrease PPG (++) (N/A)</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Momordica charantia</strong></td>
<td>Baldwa VS et al (1977)</td>
<td>Non-randomized; Blinding unclear, 2 parallel group, Short-term metabolic trial</td>
<td>9 DM (76 Type 1, 3 Type 2); all on insulin/OHA stopped during study</td>
<td>Momordica charantia vegetable insulin (purified protein extract); single severity dependent experimental dose (subcutaneous)</td>
<td>Placebo injection (unspecified)</td>
<td>Decrease FBG (++) (N/A)</td>
<td>No hyper-sensitivity reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Momordica charantia</strong></td>
<td>Russo EMK et al (1990)</td>
<td>Double-blind; Crossover</td>
<td>18 Type 2; on diet and/or OHA</td>
<td>Myrcia uniflora tea, 3g/d (1g individual tea bags from dried leaves); for 8 wks</td>
<td>Placebo herb tea (sape, Imperata brasiliensis)</td>
<td>No change in FBG, HgbA1C; decrease insulin (−) (3)</td>
<td>No side effects, no effect on liver/kidney function</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ocimum sanctum</strong></td>
<td>Agrawal Pet al (1996)</td>
<td>Single-blind; Crossover</td>
<td>40 Type 2; on diet and/or OHA</td>
<td>Ocimum album fresh leaf, 2.5g powder; for 4 wks</td>
<td>Fresh spinach leaf powder</td>
<td>Decrease FBG, PPG, urine glucose (++) (2)</td>
<td>No side effects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Review of herbs/vitamins in diabetes

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Dose</th>
<th>Study Design</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Opuntia streptacantha</em> (Nopal)</td>
<td>Fresh nopal stems, broiled; 500g crude weight; single experimental dose</td>
<td>Open-label; Crossover; Short-term metabolic trial</td>
<td>Decrease FBG, PPG, insulin requirement, C-peptide</td>
<td>Not reported</td>
</tr>
<tr>
<td><em>Silymarin</em></td>
<td>600mg/d</td>
<td>Parallel groups</td>
<td>Mean BG, urine glucose, HgbA1C, fasting insulin, insulin requirement, C-peptide</td>
<td>No treatment, decreased insulin requirement, C-peptide</td>
</tr>
<tr>
<td><em>Trigonella foenum-graecum</em> (Fenugreek)</td>
<td>15g in water; single experimental dose with meal tolerance test</td>
<td>Crossover; Short-term metabolic trial</td>
<td>Decrease FBG, PPG, fasting insulin, insulin requirement, C-peptide</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

### RESEARCH DESIGN AND METHODS

We searched MEDLINE, OLDMEDLINE, CAM-PubMed, HealthSTAR, and the Cochrane Library Database from 1960 to March 2002 using the MeSH terms CAM, alternative therapies, hypoglycemic plants, and individual herb and supplement names from popular sources, each crossed with the term diabetes mellitus. In addition, we contacted experts in the field to identify studies, and we also hand-searched references of key articles. We did not include supplements made from animal components. Fish oil supplementation, for example, has been examined in prior meta-analyses (46,47). We also did not include soluble fiber supplements, which overlap considerably with dietary fiber treatment and already play a role in conventional diabetes nutrition advice (48–51).

We limited studies to those published...
Table 2—Controlled clinical trials of combination herbs for glycemic control*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Sample</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome</th>
<th>Evidence Jadad</th>
<th>Adverse Effects</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al (2001)</td>
<td>Double-blind, 2 parallel groups</td>
<td>12 Type 2, on diet</td>
<td>Herbs+Western</td>
<td>Placebo tablet</td>
<td>No change in HgbA1c, FBG, or insulin</td>
<td>3</td>
<td>N/A</td>
<td>No side effects</td>
</tr>
<tr>
<td>Ng et al (2000)</td>
<td>Double-blind, 2 parallel groups</td>
<td>14 Type 2</td>
<td>Herbs+Western</td>
<td>Placebo tablet</td>
<td>No change in HgbA1c, FBG, or insulin</td>
<td>3</td>
<td>N/A</td>
<td>No side effects</td>
</tr>
<tr>
<td>Xiong M et al (1995)</td>
<td>Non-randomized, 1 parallel group</td>
<td>12 Type 2, on diet</td>
<td>Herbs+Western</td>
<td>Placebo extract</td>
<td>No change in HgbA1c, FBG, or insulin</td>
<td>3</td>
<td>N/A</td>
<td>No side effects</td>
</tr>
<tr>
<td>Yang et al (1998)</td>
<td>Double-blind, 1 parallel group</td>
<td>1 Type 2</td>
<td>Herbs+Western</td>
<td>Placebo tablet</td>
<td>No change in HgbA1c, FBG, or insulin</td>
<td>3</td>
<td>N/A</td>
<td>No side effects</td>
</tr>
</tbody>
</table>

*All trials are randomized unless otherwise specified in the Design column. —, no outcome measures positive; +, at least one outcome measure positive; ++, >50% of outcome measures positive; FBG, fasting blood glucose; PPG, postprandial glucose; OHA, oral hypoglycemic agent. 

**Table 2**—Controlled clinical trials of combination herbs for glycemic control.

Data synthesis

A total of 108 clinical studies were found examining 25 single herbs, 11 combination herb formulas, and 9 vitamin/mineral supplements as potential therapy for diabetes. Of these, 58 were controlled clinical trials in patients with diabetes or impaired glucose tolerance (42 randomized, 16 nonrandomized). Only four of the controlled trials included patients with type 1 diabetes (57–60). In addition, there were 12 trials examining glycemic parameters in healthy individuals. The remaining studies were 36 uncontrolled prospective cohort trials and 2 case reports.

We present the available evidence for 26 of the substances with either one or more controlled clinical trials in patients with diabetes or impaired glucose tolerance. Methodological details and results of these trials are summarized in Tables...
### Table 3—Controlled clinical trials of vitamin/mineral supplements for glycemic control*

<table>
<thead>
<tr>
<th>Herb/Supplement</th>
<th>Reference</th>
<th>Design</th>
<th>Sample</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Evidence</th>
<th>Jadad</th>
<th>Adverse Effects/Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-lipoic Acid</td>
<td>Jacob S et al (1999)</td>
<td>Blinding unclear; 4 parallel groups</td>
<td>74 Type 2; well-controlled on diet and/or OHA</td>
<td>Alpha-lipoic-acid 600 mg/d vs. 1200 mg/d vs. 1800 mg/d (Thioctacid, Asta Medica, Germany); for 4 wks</td>
<td>Placebo pill</td>
<td>Increase glucose uptake; trend decrease fasting insulin and improve insulin sensitivity; no change in FPG</td>
<td>+</td>
<td>1</td>
<td>No side effects</td>
</tr>
<tr>
<td>Branched Chain AA</td>
<td>Mourier A et al (1997)</td>
<td>Open-label; 4 parallel groups</td>
<td>24 Type 2; on diet and/or OHA</td>
<td>Branched chain amino acid supplement containing leucine, isoleucine, valine (Paraphar Laboratories, France) + (~) exercise training program; for 2 mos</td>
<td>Placebo supplement (tricalcium phosphate and stearate of magnesium)</td>
<td>No supplement effect on FBG, PPG, insulin, HgbA1C</td>
<td>-</td>
<td>2</td>
<td>No side effects</td>
</tr>
<tr>
<td>Carnitine (Acetyl-L-Carnitine)</td>
<td>Giancaterini A et al (2000)</td>
<td>Double-blind; Crossover; Short-term metabolic trial</td>
<td>18 Type 2; on diet, OHA, and/or insulin (switched to insulin during study)</td>
<td>Intravenous infusion acetyl-L-carnitine; 0.025mg/kg/min vs 0.1mg/kg/min; constant infusion during euglycemic-hyperinsulinemic clamp</td>
<td>Saline infusion</td>
<td>Increase glucose uptake, glucose storage, decrease insulin; no change in glucose or lipid oxidation</td>
<td>++</td>
<td>4</td>
<td>Not reported</td>
</tr>
<tr>
<td>Carnitine (L-Carnitine)</td>
<td>Mingrone G et al (1999)</td>
<td>Blinding unclear; Crossover; Short-term metabolic trial</td>
<td>15 Type 2; on diet and OHA (switched to insulin during study)</td>
<td>L-Carnitine; 0.28 µmol/kg bw/min (Sigma Tau S.P.A., Italy); simultaneous infusion with euglycemic-hyperinsulinemic clamp</td>
<td>Saline infusion</td>
<td>Increase glucose uptake, decrease insulin, glucose storage, insulin sensitivity</td>
<td>++</td>
<td>1</td>
<td>Not reported</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Capaldo B et al (1991)</td>
<td>Blinding unclear; Crossover; Short-term metabolic trial</td>
<td>9 Type 2</td>
<td>Carnitine; 1.7mmol/min; constant intravenous infusion with euglycemic hyperinsulinemic clamp</td>
<td>Saline infusion</td>
<td>Increase glucose uptake, insulin sensitivity</td>
<td>++</td>
<td>1</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chromium</td>
<td>Lee NA et al (1994)</td>
<td>Double-blind; Crossover</td>
<td>30 Type 2; on diet, OHA, and/or insulin</td>
<td>Chromium picolinate; 200µg/d (unspecified preparation); for 2 mos</td>
<td>Placebo pill</td>
<td>No change in FBG, HgbA1C</td>
<td>-</td>
<td>4</td>
<td>No side effects</td>
</tr>
<tr>
<td>Chromium</td>
<td>Anderson R et al (1997)</td>
<td>Double-blind; Crossover</td>
<td>180 Type 2; on diet, OHA, and/or TCM meds</td>
<td>Chromium picolinate; 200µg/d vs. 1000µg/d (“Nutrition21,” San Diego, CA); for 8 wks</td>
<td>Matched placebo pill</td>
<td>Decrease HgbA1C, fasting and postprandial insulin (both doses); decrease FPG and PPG (high dose)</td>
<td>++</td>
<td>3</td>
<td>No side effects</td>
</tr>
<tr>
<td>Chromium</td>
<td>Bahijiri SM et al (2000)</td>
<td>Double-blind; Multiple crossover</td>
<td>78 Type 2; on diet, OHA, and/or insulin</td>
<td>Organic chromium (Brewer’s yeast capsule 23.5 µg Cr/day) vs. Inorganic chromium (CrCl3 capsule 200µg Cr/day); for 8 wks</td>
<td>Torula yeast capsule</td>
<td>Decrease FPG, PPG, fructosamine (both Cr supplement types); no change in BMI</td>
<td>++</td>
<td>4</td>
<td>No side effects</td>
</tr>
<tr>
<td>Chromium</td>
<td>Uusitupa MJ et al (1992)</td>
<td>Double-blind; 2 parallel groups</td>
<td>26 elderly with impaired glucose tolerance</td>
<td>Chromium-rich yeast; 160µg/d in 4 pellets (unspecified preparation); for 6 mos</td>
<td>Identical placebo pellets</td>
<td>No change in FBG, PPG, postprandial insulin, HgbA1C, C-peptide, BMI</td>
<td>-</td>
<td>3</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chromium</td>
<td>Anderson RA et al (1991)</td>
<td>Double-blind; Crossover</td>
<td>8 impaired glucose tolerance</td>
<td>Chromium Chloride; 200µg/d (preparation unspecified); for 4 wks</td>
<td>Placebo tablet</td>
<td>Decrease FPG, postprandial insulin, glucagon</td>
<td>++</td>
<td>2</td>
<td>Not reported</td>
</tr>
<tr>
<td>Chromium</td>
<td>Cefalu WT et al (1999)</td>
<td>Double-blind; 2 parallel groups</td>
<td>29 obese nondiabetic at risk for Type 2</td>
<td>Chromium picolinate; 1000µg/d (preparation unspecified); for 8 mos</td>
<td>Placebo</td>
<td>Increase insulin sensitivity by FSTIVGTT; no change in FPG, PPG, glycated Hgb, fructosamine, weight; trend decrease insulin</td>
<td>+</td>
<td>2</td>
<td>No side effects</td>
</tr>
<tr>
<td>Supplement</td>
<td>Authors</td>
<td>Study Design</td>
<td>Participants</td>
<td>Protocol</td>
<td>Placebo</td>
<td>Primary Outcome</td>
<td>Notes</td>
<td></td>
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<tr>
<td>Chromium</td>
<td>Abraham AS et al (1992)</td>
<td>Double-blind; 2 parallel groups</td>
<td>25 Type 2 with atherosclerotic disease, on diet and/or OHA</td>
<td>Chromium chloride; 230 μg/d in syrup (preparation unspecified), for 7–16 mos</td>
<td>Placebo supplement in syrup</td>
<td>No change in FBG</td>
<td>2 No side effects, no effect on liver/renal function tests, CBC, chemistries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium, Zinc</td>
<td>Anderson RA et al (2001)</td>
<td>Double-blind; 4 parallel groups</td>
<td>110 Type 2, well-controlled on diet, OHA, and/or insulin</td>
<td>Chromium picolinate 400 μg/d vs. Zinc gluconate 30 mg/d vs. Zn + Cr (Lab factorial Pharmaceutical, France), for 6 mos</td>
<td>Placebo pill</td>
<td>Decrease in plasma thiobarbituric acid reactive substances (TBARS), no change in FPG, HgbA1C, insulin, weight, BMI (all supplement groups)</td>
<td>2 No side effects</td>
<td></td>
<td></td>
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<tr>
<td>Mg</td>
<td>de Lourdes LM et al (1988)</td>
<td>Double-blind; 3 parallel groups</td>
<td>128 Type 2, poorly controlled with neuropathy and CAD on diet and/or OHA</td>
<td>Magnesium oxide; 20.7 mmol/d vs. 4.1 mmol/d elemental Mg, for 30 d</td>
<td>Placebo pill</td>
<td>Decrease fructosamine (higher dose); no change in FBG, HgbA1C, BMI</td>
<td>3 No side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>Eibl NL et al (1995)</td>
<td>Double-blind; 2 parallel groups</td>
<td>40 Type 2 with hypomagnesemia, well-controlled on diet and OHA</td>
<td>Magnesium citrate; 30 mmol/d (Magnes petrolatum, Asta Medica), for 3 mos</td>
<td>Placebo pill</td>
<td>No change in HgbA1C, FBG, PPG, insulin</td>
<td>3 Exanthem (1), gastrointestinal pain (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>Paolisso G et al (1992)</td>
<td>Double-blind; Crossover</td>
<td>12 nondiabetic (elderly with insulin resistance)</td>
<td>Magnesium picolinate; 4.5 g/d Mg, (“Mag2,” Lirca Synthelabo, Italy), for 4 wks</td>
<td>Placebo pill</td>
<td>Decrease FBG, increase postprandial insulin, glucose uptake, glucose oxidation; unclear C-peptide</td>
<td>++ 2 Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>Paolisso G et al (1994)</td>
<td>Double-blind; Crossover</td>
<td>9 Type 2, elderly, nonobese, on diet alone</td>
<td>Magnesium picolinate; 4.5 g/d (“Mag2,” Lirca Synthelabo, Italy), for 4 wks</td>
<td>Placebo pill</td>
<td>Improve insulin sensitivity and glucose oxidation during clamp; no change in FPG, C-peptide, glucagon, body weight</td>
<td>+ 2 Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>de Valk HW et al (1998)</td>
<td>Blinding unclear; 2 parallel groups</td>
<td>50 Type 2, all on diet and insulin</td>
<td>Magnesium aspartate HCL; 15 mmol/d (Verla-Pharm, Germany), for 3 mos</td>
<td>Placebo</td>
<td>No change in FBG, HgbA1C, urine glucose</td>
<td>2 No side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>Paolisso G et al (1999)</td>
<td>Open-label; Crossover</td>
<td>8 Type 2, on diet and OHA (diet alone during study)</td>
<td>Magnesium 2gm/d (“Mag2,” Lirca Synthelabo, Italy), for 4 wks</td>
<td>Placebo pill</td>
<td>Decrease FPG, increase postprandial insulin</td>
<td>++ 1 Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg, Vit C</td>
<td>Eriksson J et al (1995)</td>
<td>Double-blind; Crossover</td>
<td>29 Type 1, 27 Type 2, on diet, OHA and/or insulin</td>
<td>Magnesium (600 mg/day) vs. Ascorbic Acid (2 g/day) water soluble tablets, for 90 d</td>
<td>No treatment</td>
<td>Decrease FBG, HgbA1C (Vit C in Type 2 only), otherwise no change</td>
<td>– 3 No side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanadium</td>
<td>Cohen N et al (1995)</td>
<td>Non-randomized; Single-blind; Crossover</td>
<td>6 Type 2, diet and/or OHA</td>
<td>Vanadyl sulphate hydrate; 100 mg/day (Spectrum Chemical, CA), for 3 wks</td>
<td>Placebo capsule</td>
<td>Decrease FBG, HgbA1C, hepatic glucose production; increase insulin-mediated glucose uptake, insulin sensitivity; trend decrease fructosamine; no change PPG and C-peptide</td>
<td>++ N/A 5/6 transient gastrointestinal discomfort, no effect on liver/kidney function</td>
<td></td>
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<tr>
<td>Vanadium</td>
<td>Halberstam M et al (1996)</td>
<td>Non-randomized; Single-blind; Crossover</td>
<td>7 Type 2</td>
<td>Vanadyl sulphate hydrate; 100 mg/day (Spectrum Chemical, CA), for 3 wks</td>
<td>Placebo capsule</td>
<td>Decrease FBG, HgbA1C, hepatic glucose output; increase insulin sensitivity; no change in insulin</td>
<td>++ N/A 7/7 transient gastrointestinal discomfort no effect liver/kidney function</td>
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### RESULTS

#### Single herbs/plant derivatives for glycemic control

Table 1 presents the controlled clinical trials of single herbs for glycemic control in patients with diabetes. Of the single herbs studied, the higher-quality RCTs (with Jadad scores of 3 or greater) are available for *Coccinia indica*, ginseng species, *Bauhinia forficata*, and *Myrcia uniflora*. One RCT for *Allium sativum* is also of adequate quality but was conducted in nondiabetic individuals. Other herbs, *Allium cepa*, *Ocimum sanctum*, *Ficus carica*, *Silibum marianum*, *Opuntia streptacantha*, and *Trigonella foenum-graecum* have been studied in poorer-quality RCTs. *Gymnema sylvestre* and *Momordica charantia* have been studied in only nonrandomized controlled trials.

#### Coccinia indica

*Coccinia indica* (ivy gourd) is a creeping plant that grows wildly in many parts of the India subcontinent, and is used to treat "sugar urine" (madhumeha) in Ayurveda, a traditional East Indian healing system. The mechanism of action of
Coccinia indica is not well understood, but the herb appears to have insulin-mimetic properties (61–63). The one RCT of this herb (n = 32), conducted in India, reported significant changes in glycemic control following 6 weeks’ use of powder from locally obtained crushed dried leaves in poorly controlled or otherwise untreated patients with type 2 diabetes (64). Another three-arm controlled clinical trial (n = 70) compared 12 weeks’ use of dried herb pellets made from fresh leaves with no treatment and oral hypoglycemic agents (chlorpropamide) in patients with type 2 diabetes (61). The magnitude of change seen with the herb was similar to that with a conventional drug. Two other open-label prospective trials offer supporting evidence of a hypoglycemic effect (62,63). No adverse events were reported in these trials. The preliminary evidence suggests that the potential role for Coccinia indica in diabetes warrants further study. (U.S. Preventive Services Task Force Level I, American Diabetes Association Guidelines Level A)

Ginseng species

Several different plant species are often referred to as ginseng. These include Chinese or Korean ginseng (Panax ginseng), Siberian ginseng (Eleutherococcus senticosus), American ginseng (P. quiquefolius), and Japanese ginseng (P. japonicus). Panax species (from the root panacea) are often touted for their “cure-all” adaptogenic properties, immune-stimulant effects, and their ability to increase stamina, concentration, longevity, and overall well-being (37). Preparations use the herb’s root; some sources report greater efficacy with roots that are greater than 3 years old. Principal components are believed to be the triterpenoid saponin glycosides (ginsenosides or panaxosides). Hypoglycemic effects have been shown in streptozotocin rat models (65). Reported mechanisms of action include decreased rate of carbohydrate absorption into the portal hepatic circulation, increased glucose transport and uptake mediated by nitric oxide, increased glycogen storage, and modulation of insulin secretion (39).

Most clinical trials we found utilized American ginseng, with many examining the herb’s short-term effects on patients with type 2 diabetes after a standard oral GTT (66,67). Two longer-term trials administered American ginseng for 8 weeks (n = 36 and n = 24); both reported decreases in fasting blood glucose and HbA1c (68,69). Only one case of insomnia was reported in these trials. Three other short-term metabolic trials in healthy volunteers also found decreases in postprandial glucose (66,70,71). All but one of the clinical trials we examined were from the same investigator group. The available evidence for American ginseng in diabetes suggests a possible hypoglycemic effect; however, the trials are small and longer-term studies are needed. (Level I, A)

Allium species: sativum and cepa

Allium sativum (garlic), a member of the lily family, is most commonly used worldwide for flavorful cooking. Much of the clinical literature on garlic has focused on its potential antioxidant activity and microcirculatory effects (e.g., allicin and ajoene for use in hypertension and hyperlipidemia). Few studies have examined its effects on insulin and glucose handling, although some attention has been given to allyl propyl disulfide, a volatile oil, and S-allyl-cysteine sulfoxide, a sulfur containing amino acid (39,72). Experiments in animal models with alloxan-induced diabetes have shown moderate reductions in blood glucose; no effect is seen in pancreatectomized animals (72,72). Allium cepa (onion) also contains allyl propyl disulfide and has similar purported hypoglycemic properties. Reported mechanisms of allium species include increased secretion or slowed degradation of insulin, increased glutathione peroxidase activity, and improved liver glycogen storage (39,41).

The highest quality RCT of Allium sativum in humans was actually designed to examine thrombocyte aggregation in nondiabetic individuals (n = 60). However, the investigators found significant decreases in fasting serum glucose (74). The only available trial of garlic in patients with type 2 diabetes (n = 33) did not find consistent glucose or insulin responses after 1 month of supplementation (75). The only clinical trial available for Allium cepa is a small RCT of allyl propyl disulfide extract capsules from onion in nondiabetic volunteers (n = 6); investigators showed an acute decrease in fasting blood glucose and increase in insulin, supporting an insulin-mediated effect (76). No adverse events were reported in these trials. The limited data provide conflicting evidence for allium species in glycemic control. (Level I, C)

Ocimum sanctum

Ocimum sanctum (holy basil) is another commonly used herb in Ayurveda (related species include Ocimum album and Ocimum basilicum). Studies in animal models suggest hypoglycemic effects (77), although the mechanism of action remains unknown. Postulated effects include enhanced β-cell function and insulin secretion. The one available controlled clinical trial of Ocimum sanctum (n = 40) showed positive effects on both fasting and postprandial glucose in patients with type 2 diabetes using a local preparation of fresh leaf powder mixed in water for 4 weeks (78). No adverse effects were reported. Further information is needed before the efficacy of Ocimum sanctum in diabetes can be fully assessed. (Level III, C)

Trigonella foenum graecum

Trigonella foenum graecum (fenugreek) is a legume extensively cultivated in India, North Africa, and the Mediterranean. It is a common condiment used in Indian cooking and commonly used herb in Ayurveda. Defatted seeds of fenugreek, which are rich in fiber, saponins, and protein, have been described in early Greek and Latin pharmacopoeias for hyperglycemia. Although the seed portion is often mentioned, other parts of the herb have also been investigated. Purported mechanisms include delay of gastric emptying, slowing carbohydrate absorption, and inhibition of glucose transport from the fiber content, as well as increased erythrocyte insulin receptors and modulation of peripheral glucose utilization. Many studies in alloxan-rat models have shown modulated excocrine pancreatic secretion (79).

There are several trials available for fenugreek in type 2 diabetes; however, most are noncontrolled (158). Of the available RCTs, they are generally poorer-quality studies with small numbers (n = 5–15) and from a single investigator group. Nonetheless, these trials, including a single trial in type 1 diabetes, have reported improved glycemic control using seed powder incorporated into unleavened bread (59,80). Another trial in healthy volunteers (n = 38) incorporated several short-term randomized crossover experiments administering different
preparations of fenugreek before oral GTT. In these series of trials, whole raw seeds, extracted seed powder, gum isolate of seeds, and cooked whole seeds seemed to decrease postprandial glucose levels, whereas degummed seeds and cooked leaves did not (79). Other open-label prospective cohort studies have followed patients on fenugreek for up to 6 months with reported benefits in glycemic control (79.81–84). No adverse effects were reported in these trials. There is some preliminary evidence for the efficacy of fenugreek that suggests further studies may be warranted. (Level II-2, C)

_Bauhinia forficata_ and _Myrcia uniflora_

Indigenous to rainforests and tropical areas of South America, _Bauhinia forficata_ has been used in traditional treatment of diabetes in that area. In Brazilian herbal medicine, Bauhinia species have been referred to as “vegetable insulin.” Another commonly used South American herb is _Myrcia uniflora_. As part of a national effort to identify potential plant species useful in glucose control, two small crossover studies (n = 16 and n = 18) by one investigator administered each of these herbs as tea infusions to separate groups of patients three times daily for 8 weeks. No significant differences in glucose or HbA1c were detected between study herb infusion and a placebo tea using _Imperata brasiliensis_. No adverse effects were reported (85). This limited preliminary evidence does not support the hypoglycemic effect of these two plant species. (Level I, American Diabetes Association level not applicable if no studies show benefit)

_Ficus carica_

_Ficus carica_ (fig leaf) is a popular plant used for patients with diabetes in Spain and other areas in Southwestern Europe. Its active component is unknown. Several studies in animal models with diabetes have shown both short- and long-term hypoglycemic effects, although human trials are lacking. Potential hypolipidemic effects in diabetic rats have also been shown (86–88). Its mechanism for glucose effect is unknown; however, some studies suggest facilitation of glucose uptake peripherally. The one available clinical trial is a small crossover study of fig leaf tea for 4 weeks in patients with type 1 diabetes (n = 10); investigators showed a decrease in postprandial glucose and insulin requirements, but no change in fasting glucose when compared with the control commercial tea (60). No effect was seen in C-peptide levels, thereby supporting a non–insulin-mediated effect. No adverse effects were reported. Clearly, more information is needed before the efficacy of _Ficus carica_ can be properly assessed. (Level III, C)

_Opuntia streptacantha_

_Opuntia streptacantha_ (nopal) or the prickly pear cactus can be found in arid regions throughout the Western hemisphere, including the southwestern U.S., and is commonly used for glucose control by those of Mexican descent. It has a high-soluble fiber and pectin content, which may affect intestinal glucose uptake, partially accounting for its hypoglycemic actions (65). Animal models have reported decreases in postprandial glucose and HbA1c, with synergistic effects with insulin. Studies in pancreatectomized animals report that hypoglycemic activity is not dependent on the presence of insulin (89). Most human studies of nopal have been published in Spanish and, thus, are not included in this review. We found only two controlled short-term metabolic trials (n = 14 and n = 32) published in the English language, both by the same investigator (90,91). These reported improvements in patients with type 2 diabetes with decreased fasting glucose and decreased insulin levels, suggesting enhanced insulin sensitivity. No side effects were reported in these trials. The limited data suggests a possible hypoglycemic effect of nopal; however, longer-term clinical trials are needed. (Level III, C)

_Silibum marianum_

_Silibum marianum_ (milk thistle), a member of the aster family, has been primarily studied for its purported effects on alcoholic and viral hepatitis, rather than for glycemic control. However, silymarin is rich in flavonoids, potent antioxidants, and some have postulated a potential benefit for those who have insulin resistance secondary to hepatic damage (39). Mechanisms are based on the herb’s antioxidant activity and effects on hepatocyte stabilization with decreased glutathione oxidation, as well as on restoration of normal malondialdehyde concentrations.

The one available clinical trial examined cirrhotic patients with type 2 diabetes (n = 60) using a commercially available preparation (“Legalon”) 600 mg/day; IBI Lorenzini, Milan, Italy) for 12 months, with significant improvements in glycemic control when compared with no treatment (92). No adverse effects were reported. Further information and higher quality clinical trials are needed to further investigate milk thistle in glycemic control. (Level III, C)

_Gymnema sylvestre_

_Gymnema sylvestre_ is another commonly used herb in Ayurveda. The plant is a woody climber that grows in tropical forests of central and southern India. According to common folklore, chewing the leaves causes a loss of sweet taste, hence the popular Hindi name of the plant “gur-ma,” meaning “destroyer of sugar.” Early animal studies reported blood glucose–lowering effects in animals with residual pancreatic function, but no effect in total pancreatectomized animals. Studies of an ethanol leaf extract, GS4, in diabetic rat and rabbit models have reported regeneration of islets of Langerhans, decreases in blood glucose, and increases of serum insulin (58). Mechanism of action is unknown; postulated theories include an increase in glucose uptake and utilization, increase in insulin release through cell permeability, increase in β-cell number, and stimulation of β-cell function (39,93).

Two nonrandomized controlled clinical trials are available, both from the same investigator group. Groups of patients with type 1 diabetes (n = 64) and type 2 diabetes (n = 47) showed improved glycemic control with chronic adjunctive use of GS4 extract compared with those who received conventional treatment alone (58,94). The evidence for the beneficial effect of _Gymnema sylvestre_ in diabetes is suggestive, although inconclusive given the limited data. (Level II-1, C)

_Momordica charantia_

_Momordica charantia_ is a vegetable indigenous to tropical areas, including India, Asia, South America, and Africa, also known as balsam pear, karela (karolla), and bitter melon. Reported preparations of the herb range from injectable extracts to fruit juice to fried melon bits (39,95–97). Active components are thought to be charantin, vicine, and polypeptide-p (an unidentified insulin-like protein similar to bovine insulin). Theoretical mecha-
nisms include increased insulin secretion, tissue glucose uptake, liver muscle glyco-
gen synthesis, glucose oxidation, and decreased hepatic gluconeogenesis. Studies in alloxan-induced diabetic rabbits have suggested hypoglycemic effects (98).

Two controlled short-term metabolic trials in patients with type 2 diabetes (n = 18 and n = 9) have reported acute effects on blood glucose with Momordica charan-
tia fruit juice, as well as subcutaneous injection with Aloe gel, obtained from the inner portion of the leaves, contains the laxative anthraquinone (100). Aloe gel is preferred over the sap as the latter contains the laxative anthraquinone (100). Aloe gel, obtained from the inner portion of the leaves, contains glucosanmann, a hydrophilic fiber which may in part account for its hypoglycemic effects (39). Reports in animal models have been inconsistent (100–103). Two nonrandomized clinical trials (n = 40 and n = 76) are available from the same investigator group that reported improved fasting blood glucose with 6 weeks of juice made from aloe gel (100,104). Case reports of five type 2 diabetic individuals reported decreases in fasting blood glucose as well as HbA1c (101). No adverse effects were reported in these trials. The preliminary data suggest a potential effect of Mon-
ordica charantia in diabetes. However, further information in RCTs is needed. (Level III, C)

Multiple herb combinations for glycemic control
Table 2 presents the controlled clinical trials of multiple herb combinations for glycemic control in patients with diabetes.

Combination formulas in TCM
TCM encompasses a system of healing that has origins over 2,000 years old. It emphasizes the importance of a balanced and harmonious flow of “qi,” or “life force,” and employs diverse modalities such as acupuncture, massage, qigong, and an individualized approach to herbal medicine (20). We found few trials of TCM in the English language; most have been published in Chinese and were unavailable for this review.

One controlled clinical trial of a multiple herb combination examined a specific formulation containing Coptis chinensis, Astragalus membranaceus, and Lonicera japonica. Among a host of other plants used in TCM for the treatment of diabetes, these plants were selected for study by the Chinese Academy of Medical Science based on experiential reports of efficacy and safety. Mechanisms of action are not well reported, but may include decreasing digestive carbohydrate absorption. This formula is not thought to influence action of insulin. Using a 2×2 factorial design (n = 216) with TCM verum pill or placebo and glibenclamide verum pill or placebo, investigators reported that the two treatments together were more efficacious than either alone (114). Of 216 patients, there was one report of diarrhea and one report of dry mouth. Also, one case of hypoglycemia occurred in the combined treatment group.

A much smaller trial (n = 12) of lower quality examined another TCM preparation, Xiaoke tea. Little is written about this formulation in English literature. It appears not to affect insulin concentrations and was ineffective in rats that lack endogenous insulin. The trial did not report details about the constituents of the treatment tea, and investigators reported no difference in glycemic parameters as compared with an “ordinary” tea infusion (115). Another controlled clinical trial (n = 148) examined a formulation called Semen Persical Decoction for Purgation with Addition (SPDPA), a combination of eight different herbs and reported decreases in fasting blood glucose not significantly different from changes seen with glyburide (116). No adverse effects were reported with this formulation. The available studies suggest that some TCM formulations, but not others, may have beneficial effects. However, the data are certainly limited and no formula has been studied in more than one trial. (Level I, C)

Combination formulas in Native American medicine
Native American medicine refers to the healing practices from the people indigenous to North America; the approach combines awareness of mind, body, and spirit and ritualistic observances with practices of herbalism. One clinical trial (n = 40) specifically examined an herbal tea preparation containing Populus tremuloides (trembling aspen) and Heracleum lanatum (cow parsnip) prescribed by an Alexis band Sioux healer (117). Investigators reported no glycemic benefit over a control tea containing mint and fennel seed. Little is known scientifically about this formula, and it has not been studied elsewhere. The limited evidence for this Native American herb preparation does not support its use in glycemic control. (Level I, American Diabets Association level not applicable if studies show no benefit)

Combination formulas in Tibetan medicine
Tibetan medicine is a traditional system of healing that has influences from China, Persia, India, and Greece, incorporating concepts from Ayurveda as well as psychological, philosophical, and spiritual aspects of Buddhism. Herbalism, espe-
cially from the Himalayas, plays an important role. Although of poorer quality, one large RCT (n = 200) was available that examined individualized Tibetan herb prescription based on age, sex, personality, pulse, and urine characteristics in traditional diagnosis (118). Individual plant species and postulated mechanisms were not reported. At 6 months, the study suffered a large number of dropouts (44%); however, investigators analyzed data by intention-to-treat, and improve-
ments were nevertheless reported in fasting plasma glucose, postprandial glucose, and HbA1c values. No adverse effects were noted. These limited data are incon-
clusive regarding use of individual Tibetan herb prescriptions in type 2 dia-
betes. (Level II–2, C)

We identified six other specific combination herb formulations that have
been studied in patients with diabetes, three from Ayurveda (D-400, MA-471, and Ayush-82) (33,119–121) and three from Siddha (Chendooram, Sandanapodi, and Kadal Azhijnil) (122–125). None have been examined in RCTs—only open-label prospective cohort studies or case reports.

Vitamins/trace elements/dietary supplements for glycemic control

Table 3 presents the controlled clinical trials of vitamin/mineral supplements for glycemic control in patients with diabetes. Of the studies examining vitamin and mineral supplements for glycemic control, the higher-quality RCTs (with Jadad scores of 3 or greater) are available for chromium, magnesium, vitamin E, and L-carnitine (126–137). Vanadium has been studied in only nonrandomized controlled trials (138–140).

Chromium species

Chromium (Cr3), a trace element in its trivalent form, is required for the maintenance of normal glucose metabolism. Experimentally, chromium deficiency is associated with impaired glucose tolerance, which can be improved with supplementation (35). Most individuals with diabetes, however, are not chromium deficient. In addition to glucose control, the supplement has been studied for its effects on weight control, lipids, and bone density. Its action is linked with glucose tolerance factor (GTF), and has been shown to increase the number of insulin receptors, to enhance receptor binding, and to potentiate insulin action. Some suggest that chromium picolinate is the preferred form because it is utilized more efficiently (141).

Of the eight RCTs examining chromium in those with diabetes or impaired glucose tolerance, preparations differ and the results are mixed. Among the larger trials, one using organic chromium in brewer’s yeast (n = 78) and another using chromium chloride (n = 180) reported decreases in fasting and postprandial glucose (127,128). However, another trial by Anderson (n = 110) utilizing chromium picolinate did not find changes in glycemic control (142). One large noncontrolled open-label trial of chromium picolinate followed 833 type 2 diabetic patients in China for up to 10 months. Investigators reported a decrease in fasting and postprandial glucose and a decrease in fatigue, excessive thirst, and frequent urination (143). These studies all reported no adverse effects. A recent meta-analysis by Althuis et al. (144) that included 15 RCTs (only 4 included diabetic individuals) reported that chromium had no effect on glucose or insulin concentrations in non-diabetic subjects; however, the data among patients with diabetes were inconclusive. Althuis et al. also suggested that more trials should be performed in North America, as the generalizability of trials conducted in China is unknown given regional differences in diet and nutritional status. (Level I, C)

Magnesium

Hypomagnesemia is common in patients with diabetes, especially those with glycosuria, ketoacidosis, and excess urinary magnesium losses. Deficiency of magnesium can potentially cause states of insulin resistance. Studies have examined magnesium’s potential role in the evolution of such complications as neuropathy, retinopathy, thrombosis, and hypertension. However, its role in glycemic control is unknown. Magnesium is a cofactor for various enzyme pathways involved in glucose oxidation, and it modulates glucose transport across cell membranes. It may increase insulin secretion and/or improve insulin sensitivity and peripheral glucose uptake. It has been shown to have no effect on hepatic glucose output and nonoxidative glucose disposal (35,40). Because it is an intracellular cation, it is difficult to measure accurately, and total body stores are seldom measured.

Of the seven RCTs examining magnesium supplementation for glycemic control, only two small lower-quality trials from one investigator group (n = 8 and n = 9) reported a decrease in fasting plasma glucose and increase in postprandial insulin (145,146). Of the three highest-quality trials (Jadad score of 3), magnesium did not change blood glucose or HbA1c (130–132). One trial (n = 128) did find a decrease in serum fructosamine, a short-term marker of glycemic control. Another study (n = 40) reported one subject with an exanthem and one who had transient gastrointestinal pain with magnesium supplementation. (Interestingly, the trial by Eriksson and Kohvakkula [132] contained a study arm that administered vitamin C supplements, which unlike magnesium, did show improvements in glycemic control. To our knowledge, this is the only report of vitamin C for glucose control.) The available data for magnesium are mixed, and thus the evidence for efficacy in diabetes is inconclusive. (Level I, C)

Vitamin E

Diabetes produces a state of increased free radical activity. The purported effects of vitamin E on glucose control relate to the vitamin’s potent lipophilic antioxidant activity, with possible influences on protein glycation, lipid oxidation, and insulin sensitivity and secretion. Through unknown mechanisms, it may also affect nonoxidative glucose metabolism (35,40).

Of the controlled trials that examined vitamin E for glycemic control, the direction of the evidence for patients with type 2 diabetes is positive in four of six, with doses ranging from 100 to 1,600 mg/day for 2–4 months’ supplementation. The largest of these trials (n = 53), however, was a double-blind placebo-controlled crossover trial that found no change in serum glucose, fructosamine, or HbA1c (136). One clinical trial examined patients with type 1 diabetes (n = 35) and reported decreases in protein glycosylation after 3 months of low-dose 100 IU/day vitamin E (57). Thus far, the available evidence for vitamin E in glycemic control is mixed and inconclusive. (Level I, C)

L-Carnitine

Several in vitro studies have helped to elucidate L-carnitine’s role in metabolism, suggesting that it acts as a modulator of fuel substrate utilization in cells, influencing free fatty acid and glucose oxidation. Few have examined it clinically in patients with diabetes. Three small controlled short-term metabolic trials examined the acute effects in type 2 diabetes (n = 18, n = 15, and n = 9), showing that intravenous carnitine (or its derivative acetyl-L-carnitine) administration can possibly effect insulin sensitivity and enhance glucose uptake and storage (137,147,148). There are no longer-term clinical studies of L-carnitine for glucose control and no studies of orally administered preparations. Thus, the available data are limited, and no conclusions can be made regarding its possible use in diabetes management. (Level I, A)
Vanadium
Vanadium has been described as either a nonessential nutrient or a nutrient that is required only in minute quantities, as no physiological role of the trace element has yet to be found (35,149). Human deficiency has not been documented. There are no accurate assays in clinical settings, and there is no recommended daily allowance. Vanadium exists in several valence forms, with vanadyl (+5) sulfate and sodium metavanadate (+4) being the most common supplement forms. Its mechanism of action in glycemic control is thought to be primarily insulin-mimetic with upregulation of insulin receptors. In animal models, it has been shown to facilitate glucose uptake and metabolism and to enhance insulin sensitivity. Clinically, it may enhance glucose oxidation and glycogen synthesis, and it may modulate hepatic glucose output (35). Three very small controlled clinical trials (n = 6–8) have reported decreased fasting blood glucose (138–140); two of these trials also reported significant changes in HbA1c and insulin sensitivity (138,139). Two noncontrolled open-label studies, also with small sample sizes, nonetheless offer supporting evidence (150,151). Goldfine et al. (151) included type 1 diabetic patients (n = 5) who decreased their insulin requirements after 2 weeks of treatment. Gastrointestinal discomfort, including diarrhea, nausea, and flatulence, was reported by a large proportion of patients in all the vanadium trials. Organically chelated compounds, however, are thought to cause less gastrointestinal irritation than vanadium salts (149). The evidence for efficacy of vanadium in glucose control is suggestive, but as yet no RCTs are available. (Level II-1, C).

α-Lipoic acid
Also known as thioctic acid, a disulfide compound synthesized in the liver, α-lipoic acid is a potent lipophilic antioxidant. It is a cofactor in many multienzyme complexes and may also play a role in glucose oxidation (152). Experimental in vitro data have shown possible effects in enhancing glucose uptake in muscle and preventing glucose-induced protein modifications. One multiple-dosage controlled trial is available in patients with type 2 diabetes (n = 74), and it reported positive effects on glucose uptake and insulin sensitivity with 600–1,800 mg/day α-lipoic acid for 4 weeks; however, the trial showed no changes in fasting blood glucose (153). Another noncontrolled trial offers supportive evidence for a change in insulin sensitivity (152). The available data are limited and suggest that further elucidation of α-lipoic acids actions is needed. (Level II-3, C)

DISCUSSION — A total of 108 human trials of herbs and vitamin/mineral supplements for glycemic control were obtained. Most trials examined supplements as an adjunct to conventional treatment with diet and/or medication. Of the available trials, 58 were controlled (42 RCTs) and conducted specifically in individuals with diabetes or impaired glucose tolerance. Among these controlled trials, statistically significant treatment effects were reported in 88% (23 of 26) of those examining single herbs, 60% (3 of 5) of those examining combination herbs, and 67% (18 of 27) of those examining vitamin and mineral supplements. However, many trials were of poor quality. More than half of the RCTs (24 of 42, 57%) scored 2 or less on the Jadad scale. (No RCT achieved a score of 5.) Thirteen trials had sample sizes of 10 or fewer patients. In addition, there were generally few trials per supplement, making it difficult to draw definitive conclusions regarding efficacy. Nevertheless, no major safety concerns were reported in these trials. Few mild adverse effects, mainly gastrointestinal irritation, were reported for ginseng, Native American herb tea, TCM pill, magnesium, and vanadium (see Tables). For the following supplements, >50% of controlled clinical trials (at least two trials) suggested efficacy: Coccinia indica, Trigonella foenum, American ginseng, nopal, Gymnema sylvestre, Aloe vera, Mordica charantia, chromium, and vanadium. Of these, the best evidence is available for Coccinia indica and American ginseng. Supplements that appear effective but have only been studied in nonrandomized trials include Gymnema sylvestre, Aloe vera, and vanadium. Supplements that appear to be effective in short-term metabolic trials include Mordica, nopal, and l-carnitine.

Guidelines for clinicians
In assessing the quality of the evidence, we employed the American Diabetes Association criteria for clinical guidelines (55). The evidence for the majority of supplements earned a C level rating, mostly for supportive evidence from RCTs with methodological flaws or uncontrolled studies, or conflicting evidence with weight supporting the recommendation (online appendix B). Those supplements that earned an A rating include Coccinia indica, American Ginseng, and l-carnitine, with supportive evidence from at least one adequate RCT. However, according to the criteria described by Weiger et al. (56), no herb or supplement has sufficient evidence to actively recommend or discourage its use among patients with diabetes. That is, evidence regarding efficacy is inconclusive or not rigorous enough to meet the outlined requirements of efficacy, yet the herb or supplement appears to be generally safe. Physicians should thus keep an open mind in advising patients who might already be using these supplements.

The American Diabetes Association and the American Dietetic Association do not have specific recommendations for the use of herb or vitamin/mineral supplements in people with diabetes. Broad recommendations for the general public are that healthy people at low risk for nutritional deficiencies meet their requirements with natural food sources. Those at increased risk for deficiencies, such as the elderly, strict vegetarians, those following very low-calorie diets, and other special populations, may benefit from multivitamin supplements (35).

Despite the lack of formal recommendations, the American Diabetes Association has acknowledged patient interest and use of CAM supplements for diabetes. In A Step-by-Step Approach to Complementary Therapies and Guidelines for Using Vitamin, Mineral, and Herbal Supplements (154,155), safety is the main theme. Practical information for patients on choosing supplements is outlined (e.g., looking for products with recognized symbols of quality: USP, NF, TruLabel, Consumer Labs, etc.; looking for products with an expiration date; avoiding foreign products unless quality is known; and avoiding companies that make sensational claims or have misleading labels, etc). The American Diabetes Association also warns against combining supplements and prescription drugs without the physician’s knowledge and against stopping prescribed medication without the physician’s knowledge. They advise discontinuing supplements before medical procedures.
Review of herbs/vitamins in diabetes

(e.g., surgeries or anesthesia) and in the event of an adverse effect.

Although the trials contained in this review reported very few adverse effects, other sources mentioned potential or theoretical effects for six supplements. Theoretical cross-allergenicity was mentioned with silymarin as a member of the aster family (daisy) and Trigonella as a member of the leguminosae family (peanuts), although no actual cases have been reported. The most important potential drug-herb interaction was that of garlic or Trigonella with warfarin, as both herbs may have limited anticoagulant properties. Panax ginseng may increase risk of potassium depletion, so caution might be taken with those on laxatives or diuretics. Ginseng used in conjunction with monoamine oxidase inhibitors, phenelzine, or tricyclic antidepressants may cause an enhanced euphoric effect. Other adverse effects have been reported with Panax ginseng (Asian) (e.g., hypertension, hypotension, mastalgia, vaginal bleed, and insomnia), although the literature on diabetes has largely involved Panax quiquefolius (American). Rare topical reactions have been reported with nopal, garlic, and α-lipoic acid. Of note, one case of hypoglycemic coma has been reported with overdosage of Momordica charantia (36,37,39, www.naturaldatabase.com).

Clinical research of CAM supplements in diabetes

Currently, there is not yet sufficient evaluation of herbs, vitamins, and mineral supplements for glucose control in diabetes. Aside from relatively poor study methodological quality, this area of supplement research has been fraught with several complications.

First, the multiple constituent nature of botanical products has made standardization a challenging task. Proponents of herbal remedies caution that in standardizing to one constituent, resulting extracts may have lost a proportion of benefit as compared with the whole plant (156). Precise considerations of purity, chemical composition, and potency of derivatives may be grossly influenced by the age of the plant (especially of roots), the source location, the season of harvest, the method of drying and crude preparation, etc. In the literature we examined, several herb studies used “homemade” or otherwise unspecified preparations. Although individual companies have begun to standardize supplements, there is a general lack of consistency across the market. With vitamin and mineral supplements, these issues are less relevant.

In addition, the development of proper supplement regulation and safety codes has been slow. Currently, all dietary supplements (including herbal products) are regulated under the Dietary Supplement Health and Education Act of 1994 (DSHEA), which specifically differentiates supplements from drugs. Consequently, DSHEA does not require the extensive premarket approval that the Food and Drug Administration requires for a prescription drug, and although it calls for “good manufacturing practices [GMP],” the burden of proof that a supplement is unsafe lies with the government, leaving manufacturers to operate unchecked. This has contributed to skepticism among clinicians, and makes it especially difficult for physicians to responsibly recommend supplements to patients. In the absence of external regulation, the industry has taken steps to police itself. For example, the National Nutritional Foods Association (NNFA), representing about one-third to one-half of retailers and manufacturers of natural products in the U.S., has encouraged the adoption of strict, self-imposed GMP standards, as well as initiatives such as the TruLabel program (in which products are subjected to random laboratory testing by independent third-party auditors to verify contents) (42).

Research of vitamin and mineral supplements has also been hindered by a lack of accurate and meaningful assays that detect functional micronutrient deficiencies. In the case of chromium, for example, it is postulated that supplementation of targeted individuals might be more beneficial. Some speculate that positive results seen in large studies in diabetic patients in China may be due to the population’s relative chromium deficiency. However, without reliable assays, these theories have remained difficult to test (144).

Finally, the existing literature in this area includes a considerable amount of study population heterogeneity. Future research may need to more precisely define targeted diabetic populations with regard to disease classification, severity, optimal adjunctive interventions, and perhaps nutrient deficiencies. It will also be important to further elucidate mechanisms of action so that applicability to type 1 or type 2 diabetes can be clarified.

CONCLUSIONS — As interest in the potential benefit of herbs and supplements for diabetes grows, it will become increasingly important to monitor the progress of the clinical literature and to communicate these findings to patients. Based on this review, there is insufficient evidence to actively recommend or discourage use of any particular supplement, although most appeared to be generally safe. Preliminary evidence of several herbs and supplements suggest that further RCTs may be warranted. The seven most promising supplements include Coccinia indica, American ginseng, Momordica charantia, nopal, l-carnitine, Gymnema sylvestre, Aloe vera, and vanadium. Until more definitive studies help to clarify our questions, clinicians should remain cautious, yet open-minded, regarding adjunctive use of these supplements. They should be guided not only by sound clinical judgement, but also by patients’ preferences, needs, and values. As we further our understanding of herbs and dietary supplements, we might begin to develop a framework for a medical system capable of incorporating those complementary therapies proven to be beneficial.

Addendum — Since our review of this topic, the report of a large multicenter trial (n = 3,654), which examined the effects of vitamin E with and without ramipril in high-risk patients with diabetes, has been published. Although this study was primarily concerned with cardiovascular events and mortality, it does report that there were no differences in change of HbA1c between groups (157).

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