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 *Coccinia indica* 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

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Abbreviations: CAM, complementary and alternative medicine; GTT, glucose tolerance test; RCT, randomized controlled trial; TCM, Traditional Chinese medicine.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Controlled clinical trials of single herbs for glycemic control

Herb/Supplement	Reference	Design	Sample	Intervention	Control	Outcomes	Evidence Direction	Jadad	Adverse Effects/ Events
Allium sativum (Garlic)	Sitprija S et al (1987)	Double-blind; 2 parallel groups	33 Type 2; diet alone	Garlic; 700 mg/d (preparation unspecified); for 4 wks	Placebo	No change in FBG, PPG; insulin	–	2	No side effects; no effect on liver function
Aloe vera	Bunyapraphatsara N et al (1996)	Non-randomized; Single-blind; 2 parallel groups	76 Type 2; uncontrolled on OHA	Aloe vera Linn. 80% juice; 1 tbsp BID (prepared by Faculty of Pharmacy, Mahidol University, Thailand); for 42 d	Placebo juice	Decrease FBG	+	N/A	No effects on liver/ kidney function
Aloe vera	Yongchaiyudha S et al (1996)	Non-randomized; Single-blind; 2 parallel groups	40 Type 2; newly diagnosed	Aloe vera Linn. 80% juice; 1 tbsp BID (prepared by Faculty of Pharmacy, Mahidol University, Thailand); for 42 d	Placebo juice	Decrease FBG	+	N/A	1/40 ketosis (group not reported)
Artocarpus heterophyllus	Fernando MR et al (1991)†	Non-randomized; Open-label; Crossover; Short-term metabolic trial	10 Type 2; no diabetes medication	Artocarpus heterophyllus; 200mg fresh leaves boiled decoction; single experimental dose prior to GTT	Distilled water	Decrease PPG	+	N/A	Not reported
Asteracanthus longifolia	Fernando MR et al (1991)†	Non-randomized; Open-label; Crossover; Short-term metabolic trial	10 Type 2; no diabetes medication	Asteracanthus longifolia; 100mg fresh leaves boiled decoction; single experimental dose prior to GTT	Distilled water	Decrease PPG	+	N/A	Not reported
Bauhinia forficata	Russo EMK et al (1990)	Double-blind; Crossover	16 Type 2; diet and/or OHA	Bauhinia forficata tea; 3g/d (1g individual tea bags from dried leaves); for 8 wks	Placebo herb tea (sape, Imperata brasiliensis)	No change in FBG, HgbA1C, insulin	–	3	No side effects; no effect on liver/ kidney function
Coccinia indica	Azad Khan AK et al (1979)	Double-blind; 2 parallel groups	32 Type 2; uncontrolled or untreated	Coccinia indica leaf; 1800 mg/d (freeze-dried powder from fresh leaves in tablets); for 6 wks	Placebo tablet	Decrease FBG, PPG	++	4	No side effects; no effect on liver/ kidney function
Coccinia indica	Kamble SM et al (1996)	Non-randomized; Open-label; 3 parallel groups	70 Type 2; other medications unclear	Coccinia indica; 6g/d (dried pellets from fresh leaves); for 12 wks	No treatment; OHA	Decrease FBG, PPG (similar to OHA)	++	N/A	Not reported
Ficus carica (Fig leaf)	Serraclara A et al (1998)	Open-label; Crossover	10 Type 1; diet and insulin	Fig leaf tea; 13g/d leaf decoction; for 4 wks	Bitter commercial tea blend	Decrease PPG, insulin requirement; no change in FPG, C peptide, HgbA1C	+	2	No side effects
Ginseng (Unspecified)	Sotaniemi EA et al (1995)	Double-blind; 3 parallel groups	36 Type 2; newly diagnosed; diet alone	Ginseng; 100mg/d vs. 200mg/d (tablet preparation Dansk Droge, Copenhagen); for 8 wks	Placebo tablet	Decrease FBG, HgbA1C (200mg); no change in BG, insulin, C-peptide during GTT	+	3	No side effects

Ginseng (American) *Panax quinquefolius*	Vuksan V et al (2000)	Single-blind; Multiple crossover; Short-term metabolic trial	10 Type 2; diet and/or OHA	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	Identical placebo capsule containing corn flour	Decrease PPG (all doses), no difference between doses or administration times	+	3	No side effects
Ginseng (American) *Panax quinquefolius*	Vuksan V et al (2000)	Single-blind; Multiple crossover; Short-term metabolic trial	9 Type 2; well-controlled on diet and/or OHA	Ground root of American Ginseng; 3g capsule (Chai-Na-Ta Corp, British Columbia); single experimental dose at varying times prior to GTT	Identical placebo capsule containing corn flour	Decrease PPG (given at 0, −40min)	+	2	Mild insomnia (1/9)
Ginseng (American) *Panax quinquefolius*	Vuksan V et al (2001)	Double-blind; Crossover	24 Type 2; diet and/or OHA	American Ginseng extract; 3g/d (standardized extract, Chai-Na-Ta Corp, British Columbia); for 8 wks	Placebo capsule	Decrease HgbA1C, FBG; no change insulin	++	2	No effect on liver/ kidney function
Gymnema sylvestre	Baskaran K et al (1990)	Non-randomized; Open-label; 2 parallel groups	47 Type 2; all on OHA	Gymnema sylvestre extract, GS4; 400 mg/d capsule; for 18–20 mos	No GS4 treatment	Decrease FBG, HgbA1C, glycosylated plasma protein, conventional medication, urine glucose; increase insulin	++	N/A	Not reported
Gymnema sylvestre	Shanmugasundaram ERB et al (1990)	Non-randomized; Open-label; 2 parallel groups	64 Type 1; all on insulin	Gymnema sylvestre extract, GS4; 400 mg/d capsule; for 2–30 mos	No GS4 treatment	Decrease FBG, HgbA1C, glycosylated plasma protein, insulin requirement, urine glucose; increase C-peptide	++	N/A	No side effects
Momordica charantia	Welhinda J et al (1986)	Non-randomized; Open-label; Crossover; Short-term metabolic trial	18 Type 2; newly diagnosed	Momordica charantia juice; homemade preparation (dose unspecified); single experimental dose prior to GTT	Distilled water	Decrease PPG	+	N/A	Not reported
Momordica charantia, V-insulin	Baldwa VS et al (1977)	Non-randomized; Blinding unclear; 2 parallel groups; Short-term metabolic trial	9 DM (?6 Type 1, 3 Type 2); all on insulin/OHA stopped during study	Momordica charantia vegetable insulin (purified protein extract); single severity dependent experimental dose (subcutaneous)	Placebo injection (unspecified)	Decrease FBG	+	N/A	No hyper-sensitivity reactions
Myrcia uniflora	Russo EMK et al (1990)	Double-blind; Crossover	18 Type 2; on diet and/or OHA	Myrcia uniflora tea; 3g/d (1g individual tea bags from dried leaves); for 8 wks	Placebo herb tea (sape, Imperata brasiliensis)	No change in FBG, HgbA1C; decrease insulin	−	3	No side effects; no effect on liver/ kidney function
Ocimum sanctum (Holy basil)	Agrawal P et al (1996)	Single-blind; Crossover	40 Type 2; on diet and/or OHA	Ocimum album fresh leaf; 2.5g powder; for 4 wks	Fresh spinach leaf powder	Decrease FBG, PPG, urine glucose	++	2	No side effects

Opuntia streptacantha (Nopal)	Frati AC et al (1990)	Open-label; Crossover; Short-term metabolic trial	14 Type 2; diet and/or OHA (diet alone during study)	Grilled nopal stems; 500g; single experimental dose	400ml H2O	Decrease glucose, insulin	++	1	Not reported
Opuntia streptacantha (Nopal)	Frati-Munari AC et al (1988)	Non-randomized; Open-label; Crossover; Short-term metabolic trial	32 Type 2; OHA stopped during study	Fresh nopal stems, broiled; 500g crude weight; single experimental dose	Water; broiled zucchini squash	Decrease FBG, insulin	++	N/A	Not reported
Silymarin (Milk Thistle)	Velussi M et al (1997)	Open-label; 2 parallel groups	60 Type 2 with cirrhosis; diet and insulin	Silymarin; 600mg/d ("Legalon" formulation, IBI Lorenzini, Milan); for 12 mos	No treatment	Decrease FBG, mean BG, urine glucose, HgbA1C, fasting insulin, insulin requirement, C peptide	++	2	No side effects
Trigonella foenum (Fenugreek)	Sharma RD et al (1990)	Blinding unclear; Crossover	15 Type 2; diet and OHA (dose decreased 20% during study)	Defatted fenugreek seed powder; 100g/day in unleavened bread; for 10 d	No treatment	Decrease FBG, PPG, postprandial insulin, urine glucose	++	1	Not reported
Trigonella foenum (Fenugreek)	Sharma RD et al (1990)	Blinding unclear; Crossover	5 Type 2; diet and OHA (dose decreased 20% during study)	Defatted fenugreek seed powder; 100g/day in unleavened bread; for 20d	No treatment	Decrease FBG, PPG, urine glucose, insulin	++	1	Not reported
Trigonella foenum (Fenugreek)	Sharma RD et al (1990)	Blinding unclear; Crossover	10 Type 1; diet and insulin (dose decreased during study)	Defatted debitterised fenugreek seed powder; 100g/d in unleavened bread; for 10d	No treatment	Decrease FBG, PPG, urine glucose; no change body weight, insulin	++	1	Not reported
Trigonella foenum (Fenugreek)	Madar Z et al (1988)	Non-randomized; Open-label; Crossover; Short-term metabolic trial	21 Type 2	Fenugreek seed powder; 15g in water; single experimental dose with meal tolerance test	No treatment	Decrease PPG; no change in insulin	+	N/A	No side effects

*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. †Fernando MR, Wickramasinghe N, Thabrew MI, Ariyananda PL, Karunanayake EH: Effect of *Artocarpus heterophyllus* and *Asteracantha longifolia* on glucose tolerance in normal human subjects and in maturity-onset diabetic patients. *J Ethnopharmacol* 31:277–277, 1991

medicine today also have natural plant origins. Among them, metformin was derived from the flowering plant, *Galega officinalis* (Goat's Rue or French Lilac), which was a common traditional remedy for diabetes (33,34). Similarly, the use of vitamin and mineral supplements for primary or secondary disease prevention is of increasing interest (35).

However, there is relatively little known regarding efficacy and safety of herb, vitamin, or other dietary supplements for diabetes. Two prior reviews by Ernst et al. (36,37) examined plants with hypoglycemic activity in humans, including 22 clinical trials (5 randomized controlled trials [RCTs]). One recent systematic review on Ayurvedic interventions was published under the auspices of the Agency for Healthcare Research and Quality (AHRQ) (38). Additionally, there have been several qualitative reviews reporting on selected supplements used in diabetes (33,35,39–45). To our knowledge, there have been no comprehensive systematic reviews incorporating vitamin/mineral supplements, in addition to herbal products, for glucose control among patients with diabetes.

Our objective was to review and summarize the literature on herbal remedies and dietary supplements for use in diabetes, to propose guidelines that may aid practitioners in advising their patients, and to provide recommendations for future research.

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 handsearched 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

Herb/Supplement	Reference	Design	Sample	Intervention	Control	Outcomes	Evidence Direction	Jadad	Adverse Effects/Events
Traditional Chinese Medicine (TCM) herb combination	Vray M et al (1995)	Double-blind; 4 parallel groups	216 Type 2; on diet alone	Traditional Chinese herbs; 21 capsules/d (each containing 150mg Coptis Chinensis, 30mg Astragalus membranaceus, 120mg Lonicera Japonica) +/− Oral hypoglycemic (glibenclamide 7.5mg/d); for 3 mos	Placebo TCM capsule; Placebo OHA tablet	Decrease FBG, decrease PPG, with synergistic effect of both treatments; no change in insulin or HgbA1C	+	3	Diarrhea (1), dry mouth (1) TCM treatment; vertigo (1), hypoglycemia (9) OHA treatment; hypoglycemia (10) OHA+TCM
Xiaoke (TCM)	Hale PJ et al (1989)	Double-blind; Crossover	12 Type 2; on diet and/or OHA	Xiaoke tea; uncharacterized herb preparation in 2.72g teabag (Home and Sutton, London), 4 infusions/d; for 4 wks	"Ordinary tea"	No change in HgbA1C, FBG, PPG, or insulin	−	3	No side effects
SPDPA (TCM) formula	Xiong M et al (1995)	Non-randomized; Open-label; 2 parallel groups	148 Type 2	"Semen Persical Decoction for Purgation with Addition" (Rhubarb, Semen Persical, Ramulus Cinnamomum, Radix Glycyrrhizae, Radix Scrophulariae, Radix Rehmanniae, Radix Ophiopogonis, Radix Astragalus); for 2 mos	OHA (glyburide)	Decrease FBG, but no difference from control	+	N/A	No side effects
Native American herb combination	Ryan EA et al (2000)	Single-blind; 2 parallel groups	40 Type 2; on diet, OHA, and/or insulin	Herbal tea; Unspecified amount, Populus tremuloides (trembling aspen) and Heracleum lanatum (cow parsnip) decoction; 250mL/d; for 10 d	Placebo decoction with Chinese green tea, mint, fennel seed	No change in PPG, fructosamine, HgbA1C	−	2	Minor gastrointestinal discomfort (1)
Tibetan Medicine herb combination	Namdul T et al (2001)	Open-label; 2 parallel groups	200 Type 2; newly diagnosed or untreated; on diet alone	Tibetan medicine herbs; individualized powder/pill combination (at least 2 of 4:Kyura-6, Aru-18, Yungwa-4, Sugmel-19); for 6 mos	No herb treatment	Decrease FPG, PPG, and GHb; no change in weight	++	2	Not reported

*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.

in the English language and restricted our search to herbs and supplements for glycemic control and symptoms of hyperglycemia. We excluded trials that primarily examined diabetic complications such as neuropathy, nephropathy, or retinopathy. We included studies in subjects with impaired glucose tolerance or those specifically at risk for diabetes (e.g., older, sedentary, obese individuals with a family history of diabetes). As supporting evidence, we also examined studies of glycemic control in healthy volunteers. To assess quality of RCTs, we employed the Jadad scale, a previously validated instrument that assesses trials based on appropriate randomization, blinding, and description of study withdrawals or dropouts (52,53). Quality of evidence for specific herbs or supplements was assessed using the U.S. Preventive Services Task Force criteria (54) (online appendix A; http://care.diabetesjournals.org) and the American Diabetes Association evidence grading system for clinical practice recommendations (55) (online appendix B). Clinical guidelines were based on the criteria developed by Weiger et al. (56) (online appendix C). These criteria place individual CAM therapies along a continuum that encompasses "recommend" (high-quality evidence supports both efficacy and safety), "accept/consider recommending" (evidence supports both efficacy and safety), "accept" (evidence regarding efficacy is inconclusive but supports safety), and "discourage" (evidence indicates either inefficacy or serious risk).

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

Herb/Supplement	Reference	Design	Sample	Intervention	Control	Outcomes	Evidence Direction	Jadad	Adverse Effects/ Events
Alpha-lipoic Acid	Jacob S et al (1999)	Blinding unclear; 4 parallel groups	74 Type 2; well-controlled on diet and/or OHA	Alpha-lipoic-acid 600 mg/d vs. 1200mg/d vs. 1800 mg/d (Thioctacid, Asta Medica, Germany); for 4 wks	Placebo pill	Increase glucose uptake; trend decrease fasting insulin and improve insulin sensitivity; no change in FPG	+	1	No side effects
Branched Chain AA	Mourier A et al (1997)	Open-label; 4 parallel groups	24 Type 2; on diet and/or OHA	Branched chain amino acid supplement containing leucine, isoleucine, valine (Paraphar Laboratories, France) +/− exercise training program; for 2 mos	Placebo supplement (tricalcic phosphate and stearate of magnesium)	No supplement effect on FBG, PPG, insulin, HgbA1C	−	2	No side effects
Carnitine (Acetyl-L-Carnitine)	Giancaterini A et al (2000)	Double-blind; Crossover; Short-term metabolic trial	18 Type 2; on diet, OHA, and/or insulin (switched to insulin during study)	Intravenous infusion acetyl-L-camitine; 0.025mg/kg/min vs 0.1mg/kg/min; constant infusion during euglycemic-hyperinsulinemic clamp	Saline infusion	Increase glucose uptake, glucose storage; decrease insulin; no change in glucose or lipid oxidation	++	4	Not reported
Carnitine (L-Carnitine)	Mingrone G et al (1999)	Blinding unclear; Crossover; Short-term metabolic trial	15 Type 2; on diet and OHA (switched to insulin during study)	L-Carnitine; 0.28 μmol/kg bw/min (Sigma Tau S.P.A., Italy);simultaneous infusion with euglycemic hyperinsulinemic clamp	Saline infusion	Increase glucose uptake, glucose oxidation, glucose storage, insulin sensitivity	++	1	Not reported
Carnitine	Capaldo B et al (1991)	Blinding unclear; Crossover; Short-term metabolic trial	9 Type 2	Carnitine; 1.7mmol/min; constant intravenous infusion with euglycemic hyperinsulinemic clamp	Saline infusion	Increase glucose uptake, insulin sensitivity	++	1	Not reported
Chromium	Lee NA et al (1994)	Double-blind; Crossover	30 Type 2; on diet, OHA, and/or insulin	Chromium picolinate; 200μg/d (unspecified preparation); for 2 mos	Placebo pill	No change in FBG, HgbA1C	−	4	No side effects
Chromium	Anderson R et al (1997)	Double-blind; 3 parallel groups	180 Type 2; on diet, OHA, and/or TCM meds	Chromium picolinate; 200μg/d vs. 1000μg/d ("Nutrition21," San Diego, CA); for 8 wks	Matched placebo pill	Decrease HgbA1C, fasting and postprandial insulin (both doses); decrease FBG and PPG (high dose)	++	3	No side effects
Chromium	Bahijiri SM et al (2000)	Double-blind; Multiple crossover	78 Type 2; on diet, OHA, and/or insulin	Organic chromium (Brewer's yeast capsule 23.3μg Cr/day) vs. Inorganic chromium (CrCl3 capsule 200μg Cr/day); for 8 wks	Torula yeast capsule	Decrease FPG, PPG, fructosamine (both Cr supplement types); no change in BMI	++	4	No side effects
Chromium	Uusitupa MIJ et al (1992)	Double-blind; 2 parallel groups	26 elderly with impaired glucose tolerance	Chromium-rich yeast; 160μg/d in 4 pellets (unspecified preparation); for 6 mos	Identical placebo pellets	No change in FBG, PPG, postprandial insulin, HgbA1C, C-peptide, BMI	−	3	Not reported
Chromium	Anderson RA et al (1991)	Double-blind; Crossover	8 impaired glucose tolerance	Chromium Chloride; 200μg/d (preparation unspecified); for 4 wks	Placebo tablet	Decrease PPG, postprandial insulin, glucagon	++	2	Not reported
Chromium	Cefalu WT et al (1999)	Double-blind; 2 parallel groups	29 obese nondiabetic at risk for Type 2	Chromium picolinate; 1000μg/d (preparation unspecified); for 8 mos	Placebo	Increase insulin sensitivity by FSIVGTT; no change in FPG, PPG, glycated Hgb, fructosamine, weight; trend decrease insulin	+	2	No side effects

Chromium	Abraham AS et al (1992)	Blinding unclear; 2 parallel groups	25 Type 2 with atherosclerotic disease; on diet and/or OHA	Chromium chloride; 250μg/d in syrup (preparation unspecified); for 7–16 mos	Placebo supplement in syrup	No change in FBG	−	2	No side effects, no effect on liver/renal function tests, CBC, chemistries
Chromium, Zinc	Anderson RA et al (2001)	Double-blind; 4 parallel groups	110 Type 2; well-controlled on diet, OHA, and/or insulin	Chromium pidolate 400μg/d vs. Zinc gluconate 30mg/d vs. Zn+Cr (Labcatal Pharmaceutical, France); for 6 mos	Placebo pill	Decrease in plasma thiobarbituric acid reactive substances (TBARS); no change in FPG, HgbA1C, insulin, weight, BMI (all supplement groups)	−	2	No side effects
Mg	de Lourdes LM et al (1988)	Double-blind; 3 parallel groups	128 Type 2, poorly controlled (with neuropathy and CAD) on diet and/or OHA	Magnesium oxide; 20.7mmol/d vs. 41.4 mmol/d elemental Mg; for 30 d	Placebo pill	Decrease fructosamine (higher dose); no change in FBG, HgbA1C, BMI	+	3	No side effects
Mg	Eibl NL et al (1995)	Double-blind; 2 parallel groups	40 Type 2 with hypomagnesemia; well-controlled on diet and OHA	Magnesium citrate; 30 mmol/d ("Magnosolv granulate," Asta Medica); for 3 mos	Placebo pill	No change in HgbA1C, FBG, PPG, insulin	−	3	Exanthem (1), gastrointestinal pain (1)
Mg	Paolisso G et al (1992)	Double-blind; Crossover	12 nondiabetic (elderly with insulin resistance)	Magnesium pidolate; 4.5g/d Mg, ("Mag2," Lirca Synthelabo, Italy); for 4 wks	Placebo pill	Decrease FBG; increase postprandial insulin, glucose uptake, glucose oxidation; unclear C-peptide	++	2	Not reported
Mg	Paolisso G et al (1994)	Double-blind; Crossover	9 Type 2, elderly, nonobese; on diet alone	Magnesium pidolate; 4.5g/d ("Mag2," Lirca Synthelabo, Italy); for 4 wks	Placebo	Improve insulin sensitivity and glucose oxidation during clamp; no change in FPG, C-peptide, glucagon, body weight	+	2	Not reported
Mg	deValk HW et al (1998)	Blinding unclear; 2 parallel groups	50 Type 2; all on diet and insulin	Magnesium aspartate HCL; 15 mmol/d (Verla-Pharm, Germany); for 3 mos	Placebo	No change in FBG, HgbA1C, urine glucose	−	2	No side effects
Mg	Paolisso G et al (1999)	Open-label; Crossover	8 Type 2; on diet and OHA (diet alone during study)	Magnesium; 2gm/d ("Mag2," Lirca Synthelabo, Italy); for 4 wks	Placebo pill	Decrease FPG, increase postprandial insulin	++	1	Not reported
Mg, Vit C	Erikksson J et al (1995)	Double-blind; Crossover	29 Type 1, 27 Type 2; on diet, OHA and/or insulin	Magnesium (600 mg/day) vs. Ascorbic Acid (2g/day) water soluble tablets; for 90 d	No treatment	Decrease FBG, HgbA1C (Vit C in Type 2 only); otherwise no change	−	3	No side effects
Vanadium	Cohen N et al (1995)	Non-randomized; Single-blind; Crossover	6 Type 2; diet and/or OHA	Vanadyl sulfate hydrate; 100mg/day (Spectrum Chemical, CA); for 3 wks	Placebo capsule	Decrease FBG, HgbA1C, hepatic glucose production; increase insulin-mediated glucose uptake, insulin sensitivity; trend decrease fructosamine; no change PPG and C-peptide	++	N/A	5/6 transient gastrointestinal discomfort; no effect on liver/kidney function
Vanadium	Halberstam M et al (1996)	Non-randomized; Single-blind; Crossover	7 Type 2	Vanadyl sulfate hydrate; 100mg/day (Spectrum Chemical, CA); for 3 wks	Placebo capsule	Decrease FBG, HgbA1C, hepatic glucose output; increase insulin sensitivity; no change in insulin	++	N/A	7/7 transient gastrointestinal discomfort no effect liver/kidney function

Vanadium	Boden G et al (1996)	Non-randomized; Single-blind; Crossover	8 Type 2; OHA and/or insulin	Vanadyl sulfate; 100mg/d; for 4 wks	Placebo capsule	Decrease FBG, decrease hepatic glucose output during clamp	++	N/A	4/8 diarrhea; 1/8 nausea; 1/8 flatulence
Vit E	Reaven PD et al (1995)	Double-blind; 2 parallel groups	21 Type 2 men; on diet and/or OHA	Vitamin E; 1600 IU/d dl-alpha-tocopherol (Hoffman-LaRoche); for 10 wks	Placebo pill	No change in FBG, PPG, postprandial insulin, glycated Hgb, glycated albumin, glycated total plasma proteins, fructosamine; decrease susceptibility of LDL to oxidation	–	4	No side effects
Vit E	Paolisso G et al (1993)	Double-blind; Crossover	15 Type 2; well controlled on diet and OHA	Vitamin E; 900 mg/d dl-alpha-tocopheryl acetate ("Ephynal," Roche, Italy); for 4 mos	Sodium citrate placebo	Decrease HgbA1C, FPG, PPG; no change in insulin, hepatic glucose output, glucose oxidation; increase total body glucose disposal and non-oxidative glucose metabolism	++	3	No side effects
Vit E	Gomez-Perez FJ et al (1996)	Double-blind; Crossover	53 DM (39 Type 2, 14 Type 1); poorly controlled on diet, OHA and/or insulin	Vitamin E; 1200 mg/d (Searle de Mexico SA de CV); for 2 mos	Placebo capsule	No change in FBG, fructosamine, HgbA1C	–	3	Not reported
Vit E	Paolisso G et al (1993)	Double-blind; Crossover	25 Type 2; well controlled on diet and OHA	Vitamin E; 900 mg/d d-alpha-tocopherol ("Ephynal," Roche, Italy); for 3 mos	Placebo pill	Decrease FPG, HgbA1C, PPG; no change in insulin	++	3	No side effects; no effect on liver/renal function tests
Vit E	Ceriello A et al (1991)	Single-blind; 3 parallel groups	30 "insulin-requiring DM"; on diet and insulin	Vitamin E; 1200mg/d vs. 600 mg/d (unspecified preparation); for 2 mos	Placebo	Decrease Hgb A1C and glycosylated protein (dose related); no change in FPG or mean daily glucose	++	1	Not reported
Vit E	Jain SK et al (1996)	Non-randomized; Double-blind; 2 parallel groups	35 Type 1	Vitamin E; 100 IU/d; for 3 mos	Placebo capsule	Decrease glycated Hgb; no change FPG, insulin requirement	+	N/A	Not reported

*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; FSIVGTT, frequently sampled intravenous glucose tolerance test; PPG, postprandial glucose; OHA, oral hypoglycemic agent.

1–3 (Single herbs, Multiple herb combinations, Vitamin and Mineral Supplements). These tables include supplement name, reference, study design, sample population, intervention, control, outcomes, direction of evidence, Jadad score, and reported adverse effects. Other studies, including some RCTs that examined glycemic parameters in healthy individuals, are not listed in the tables but are presented as supporting evidence when applicable.

The most common outcomes measures encountered in these trials included the following parameters of glycemic control: fasting and postprandial plasma glucose, response to glucose tolerance tests (GTTs), insulin and C-peptide levels, protein glycosylation (long-lived intracellular glycated hemoglobin and shorter-lived plasma fructosamine), and clinical insulin requirements. Many of the vitamin studies also examined measures of insulin sensitivity, hepatic glucose production, glucose oxidation, and glucose uptake. Oftentimes, only a few of the above measures were studied in any particular trial. A significant positive change in at least one of these important parameters was required to categorize the trial as positive.

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*, 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 HbA_{1c} (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 cepum* (onion) also contains allyl propyl disulphide 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 disulphide 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 exocrine 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 HbA_{1c} 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 hypolipdemic 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 HbA_{1c} 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 "gurmar," 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 glycogen 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 charantia* fruit juice, as well as subcutaneous vegetable insulin extract (95,99). Two other small, uncontrolled open-label trials also reported positive effects on glycemic control after longer-term use (7–11 weeks) (96,97). No adverse effects were reported in these trials. Some, albeit limited, data suggest a potential effect of *Momordica charantia* in diabetes. However, further information in RCTs is needed. (Level III, C)

Aloe vera

Aloe vera is the most well-known species of aloe, a desert plant resembling the cactus in the Liliaceae family. It is popularly used to treat burns and promote wound healing. The dried sap of the *Aloe vera* is a traditional remedy for diabetes in the Arabian peninsula (33), although 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 glucomannan, a hydrosoluble 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 HbA_{1c} (101). No adverse effects were reported in these trials. The preliminary data suggest a potential effect of *Aloe vera* in glycemic control; however, further information is needed. (Level II-1, C)

Other herbs that have been studied solely in uncontrolled trials include berberine (105), *Cinnamomym tamala* (106), curry (107), *Eugenia jambolana* (108), gingko (109), *Phyllanthus amarus* (110), *Pterocarpus marsupium* (111), *Solanum torvum* (112), and *Vinca rosea* (113).

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 Diabetes 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, especially 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 improvements were nevertheless reported in fasting plasma glucose, postprandial glucose, and HbA_{1c} values. No adverse effects were noted. These limited data are inconclusive regarding use of individual Tibetan herb prescriptions in type 2 diabetes. (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 Azhinjil) (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 pidolate 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 nondiabetic 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 generalizabiltiy 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 in 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 in diabetes, 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 HbA_{1c} (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 Kohvakka [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 glucose 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 HbA_{1c} (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 HbA_{1c} 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*, *Momordica 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 *Momordica*, 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, ConsumerLabs, 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

(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. *Momordica* 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 stimulants 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 Adminstration 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 HbA_{1c} between groups (157).

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