Dietary, Botanical, and Nutraceutical Treatments for Type 2 Diabetes

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INTRODUCTION

Type 2 diabetes has reached epidemic proportions in the US and worldwide (>18 million and 160 million individuals, respectively), and is projected to increase dramatically [1] . Furthermore, the prevalence of insulin resistance, a major causative factor in the early development of type 2 diabetes and an independent risk factor for cardiovascular disease and the metabolic syndrome X, is even more widespread [2] [3] [4] . This situation is further exacerbated by obesity, a major risk for developing type 2 diabetes. The number of adults overweight or obese in the US is 125 million (65% of population) and 1.3 billion worldwide [5] . Since dietary modification and increased physical activity provide insufficient glucose control over the long-term course of the disease, the vast majority of patients require some type of pharmacological intervention [6] .

Although pharmacological options for the management of type 2 diabetes have been increasing, and will continue to do so [7] [8] , not all patients benefit from them. In addition, the cost of prescription medications may exceed the financial capacity of an increasing number of older citizens, those without adequate health insurance, and those living in poverty [9] [10]). Furthermore, certain ethnic groups who are at increased risk for developing diabetes (e.g. Asians, Hispanics, and Native Americans), come from cultures with a long history of use of traditional medicines, and are likely to employ one or more folk (botanical) treatments rather than prescription medications [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] . Though a majority of diabetic patients are being treated, many are unable to achieve the current American Diabetes Association-recommended goal of HbA1c < 7%. Thus, in patients with poorly controlled type 2 diabetes, especially those who are obese, there is a need to identify and evaluate adjunctive therapies that are safe, efficacious, and cost-effective.

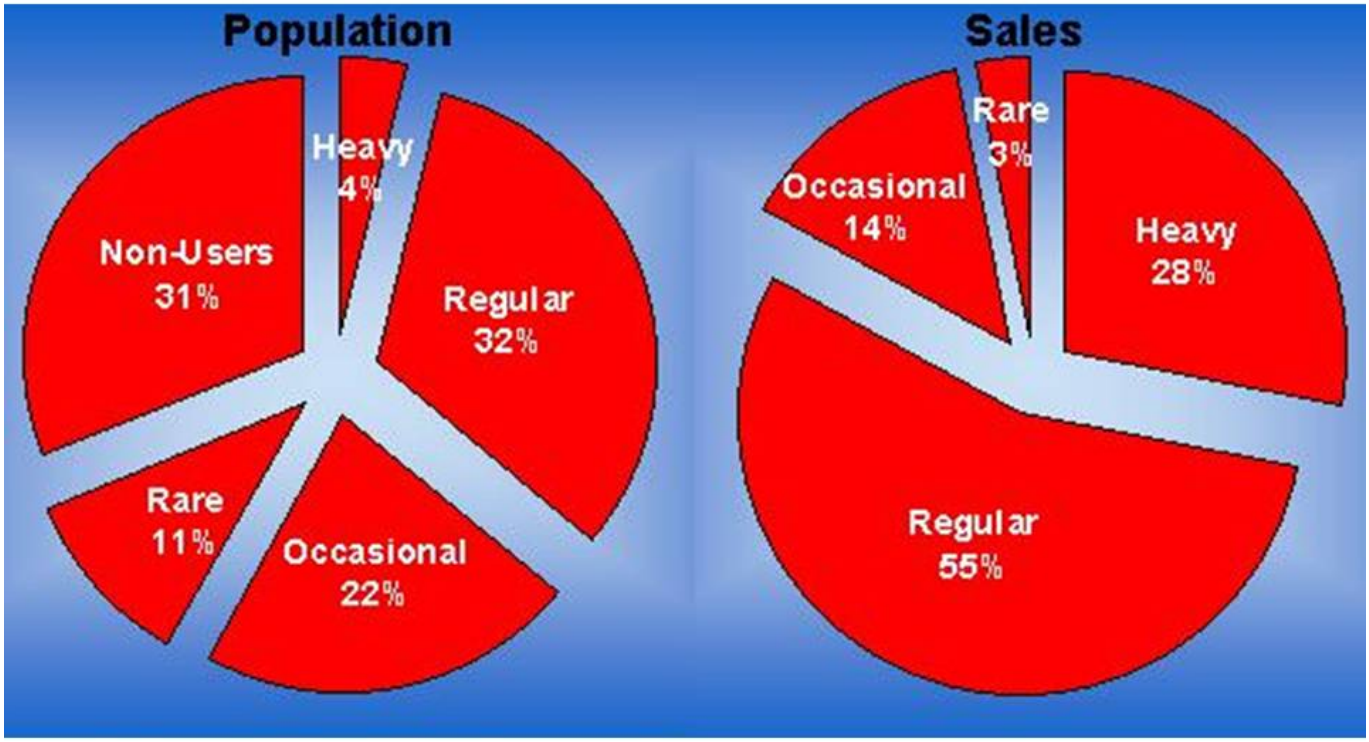
Botanical extracts, vitamins, antioxidants, minerals, amino acids, and fatty acids (natural products collectively and interchangeably referred to here as dietary supplements /

nutraceuticals) are an important source of new therapies for T2D and insulin resistance (http://nccam.nih.gov/health/diabetes /). These agents are marketed in the US under the Dietary Supplement Health and Education Act (DSHEA), passed by Congress in 1994. DSHEA defined a new category of food for regulatory purposes, termed dietary supplements, one that also includes concentrates, metabolites, constituents, extracts, and combinations, and has resulted in major changes in the marketing and use of nutraceuticals in the US (see below).

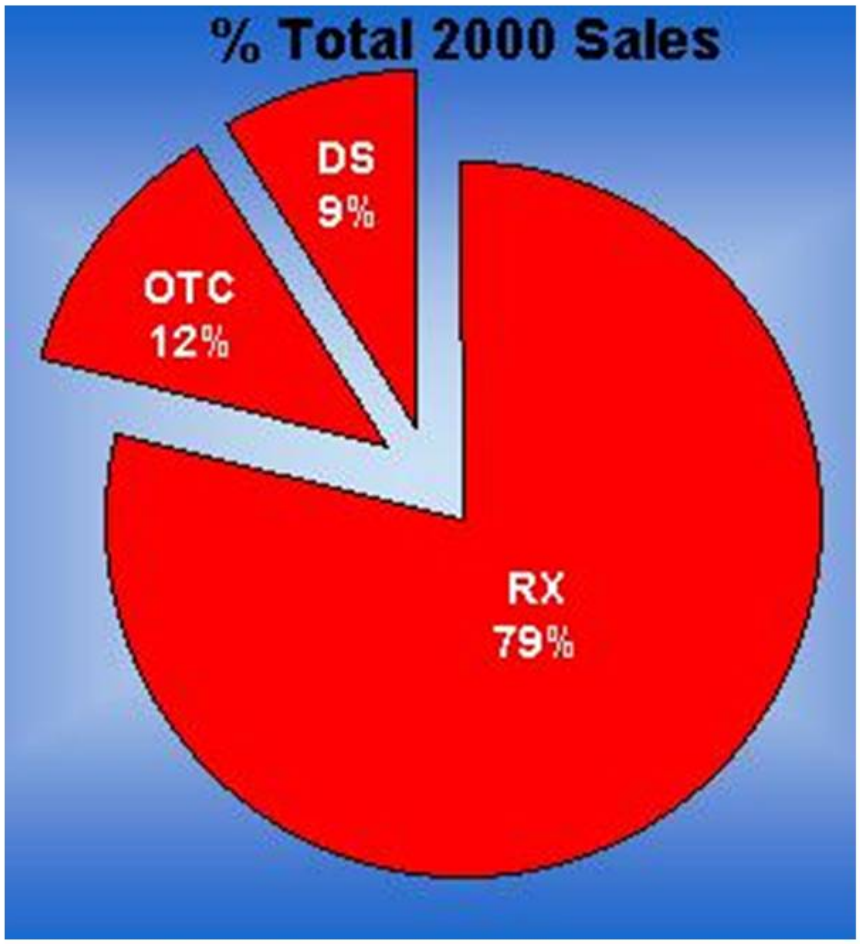
From a regulatory perspective, nutraceuticals are treated differently compared to either over the counter (OTC) or prescription pharmaceuticals [21] [22] [23] . DSHEA strictly requires manufacturers of botanicals and nutraceuticals to clearly state on all product labels that it is not intended to diagnose, treat, cure, or prevent any disease. Statements can be made to suggest that a dietary supplement enhances general health, or refers to a documented biochemical or physiological mechanism whereby a supplement affects a structure or function. These claims are commonly referred to as structure/function claims (e.g. supports cardiovascular health, immune function, etc.). In contrast to the regulatory requirements for OTC and prescription pharmaceuticals, manufacturers of dietary supplements are not required, under DSHEA, to submit evidence of safety or efficacy prior to marketing. Although a dietary supplement manufacturer is ultimately responsible for the safety of its products, the Food and Drug Administration (FDA) bears the burden of proof to show that a product is unsafe. To remove a product from the market, the FDA must be convinced that it possesses an unreasonable risk of harm at the recommended dose [24] .

For example, the increased risk for adverse events by ephredra-containing products compared with other botanicals and nutraceuticals has triggered increased pressure on the FDA to remove ephredra products from the market [25] [26] [27] [28] . A detailed comparison of the regulatory requirements of dietary supplements, OTC, and prescription medications has been recently published [29] .

Despite the caveat emptor atmosphere surrounding dietary supplements [30] , they are used by approximately 60% of the US population on at least an occasional basis (Figure 1), and constitute a significant portion of the US healthcare market (Figure 2). In 2001, US sales of botanicals and nutraceuticals were estimated at $17.6 billion (Consumer Research in the Nutrition Industry II, March 2002, Nutrition Business Journal Report, New Hope Natural Media). This figure represents approximately 33% of the total US nutrition market in 2001 (~$53 billion). The US sales in 2001 of botanicals and nutraceuticals directed towards glucose control and the resultant micro- and macrovascular complications has been estimated at approximately 2.5% of the total supplement sales or $438 million, and is expected to grow at an annual rate of approximately 10% (Condition-Specific Supplement Markets I, November 2001, Nutrition Business Journal Report, New Hope Natural Media). A recent nationally (US) representative survey has reported that over 30% of patients with diabetes used complimentary and alternative medicine (CAM) to manage their condition [31] ; in certain ethnic populations with diabetes (Navajo, Vietnamese, Hispanic), the percentages are even higher (40-66%) [32] [33] [34] [35] . In response to the increasing use of CAM by the general public [36] and by patients with diabetes [37] , the American Diabetes Association has issued a â€˜position paperâ€™ calling on health care providers to ask their patients about their use of CAM [38] .



US consumer supplement use and sales, 2001. Left panel, Estimated supplement use as percent of total US population. Right panel, Estimated supplement sales according to purchasing frequency. US sales of dietary supplements has been estimated at $17.6 billion in 2001 Figure adapted from: Consumer Research in the Nutrition Industry II, March 2002, Nutrition Business Journal Report, New Hope Natural Media).



US healthcare market sales, 2000. Distribution of total sales of $184 billion according to category. Rx, prescription drugs; OTC, over-the-counter drugs; DS, dietary supplements. Figure adapted from: Condition-Specific Supplement Markets I, November 2001, Nutrition Business Journal Report, New Hope Natural Media).

Due to the increasing use of nutraceuticals by patients with diabetes and their potential for both positive and negative impact, it is important, therefore, that diabetes health care professionals increase their knowledge of these agents [39] . To this end, several recent comprehensive reviews have focused on the use of botanicals and nutraceuticals for diabetes [40] [41] [42] [43] [44] . The overall objective of this chapter therefore is to provide a concise, comparative overview of those botanicals and nutraceuticals that have received the most scientific attention.

NUTRITIONAL INTERVENTION

Dietary modification is universally recognized by caregivers as an initial intervention and mainstay for the treatment of overweight patients with T2D [45] [46] [47] . The other side of the

non-pharmacological intervention â€˜coinâ€™ involves changes in lifestyle, usually consisting of increased physical activity [48] , smoking cessation, and reduced intake of alcohol. The overall objectives of these approaches are 1) weight loss and exercise training both resulting in improved insulin action, 2) improved glycemic and lipid control (both short-term and chronic), 3) reduced likelihood of developing microvascular and macrovascular complications, and 4) improved quality of life. It is important to remember that patients do not have to achieve their ideal body weight to reap significant health benefit. It has been reported that a loss of 10-20 lb (4.5-9 kg) will be helpful, as long as the weight loss and exercise programs are maintained [49] [50] [51] .

The recommendations of the American Diabetes Association [52] and the American Association of Clinical Endocrinologists [53] for the nutritional management of patients with T2D are provided elsewhere and will not be discussed in detail herein. The key to successful dietary intervention is to ensure that caloric intake is less than caloric output. For long-term success, this should be coupled with education designed to improve the patientâ€™s understanding of the beneficial effects of dietary modification on blood glucose, lipids, blood pressure, and overall quality of life. Some successful dietary approaches have included those designed to limit intake of saturated fats (< 7% of total caloric intake), and spreading the nutrient load. Dietary factors that are able to spread the nutrient load include increased frequency of food intake, increased intake of soluble fiber, legumes, and increased intake of foods with a low glycemic index. The beneficial role that supplements and foodstuffs high in soluble fiber play in the conventional dietary management of patients with T2D is well documented [54] [55] [56] [57] .

According to the ADA, it is unlikely that there is an optimal mix of macronutrients for the â€˜diabetic dietâ€™. The best mix of carbohydrate, protein, and fat appears to vary depending on individual circumstances. The best mix should provide a total caloric intake that facilitates, at the very minimum, weight maintenance and ideally weight loss. The average daily intake of carbohydrates recommended for patients with diabetes is approximately 45-65% of total caloric intake; low or restricted carbohydrate diets are not recommended in the management of diabetes. Intake of fat should be limited to approximately 20-35%; and dietary cholesterol should be < 200 mg/day. In patients with dyslipidemia, a special effort should be made to limit saturated fat and to substitute unsaturated or monounsaturated fat, especially omega-3 fatty acids. To reduce the risk of stroke and cardiovascular disease, diets high (3-6 servings per day) in fruits and vegetables are highly recommended [58] [59] [60] . Emerging epidemiological data suggests that higher coffee intake may reduce the risk for the development of T2D [61] . Protein intake (in patients with normal renal function) should be limited to 10-20% of total caloric intake, and reduced to 10-15% at the onset of macroalbuminuria.

With regard to micronutrient supplementation, the ADA does not recommend routine supplementation with any vitamin, mineral, or antioxidant in patients with diabetes who do not have an underlying deficiency [62] . The basis for this position is the lack of clear evidence of efficacy and, in some cases, a concern related to long-term safety [63] [64] [65] [66] [67] . With regard to alcohol intake, patients with diabetes are advised to follow the same precautions as the general population. Daily intake should be limited to a moderate amount (one drink per day or less for women, and two drinks per day or less for men). In those patients using insulin or insulin secretagogs, alcohol should be consumed with food to reduce the risk of nocturnal hypoglycemia. Alcohol alone does not acutely affect blood glucose or insulin but, if co-ingested

with carbohydrate, could raise glucose [68] .

Mediterranean Diet

Perhaps the most widely recognized diet with health promoting benefits is the so-called Mediterranean Diet. Around 50 years ago, it was recognized by Keys and associates that very low incidences of cardiovascular disease in the areas around Naples, Italy, were associated with what was soon to be termed the Mediterranean Diet [69] . The heart of this diet is mainly vegetarian, and differs from North American and Western European diets in that it is much lower in meat and dairy products, and frequently contains fruits for dessert. This diet reflects a pattern of eating most highly associated with olive growing areas of the Mediterranean. Olive oil is a critical component of this diet both because of its inherent benefits (presence of mono unsaturated fat, i.e. oleic acid) along it allowing for the consumption of high quantities of fruits and vegetables in salads and other prepared foods. Other essential components of this diet are fish (a rich source of omega-3 fatty acids; see Polyunsaturated Fatty Acids in Fatty Acid section below), nuts, wheat, grapes, and derived products including wine [70] . Many studies have convincingly demonstrated that this dietary pattern plays an important role in the prevention of cardiovascular disease [71] [72] [73] [74] [75] [76] [77] [78] .

Chocolate â€" Whatâ€™s for Dessert?

As discussed above, there is a growing body of epidemiological evidence supporting the idea that diets rich in fruits and vegetables reduce or delay the onset of many chronic diseases, including cardiovascular and related metabolic diseases [79] . A major class of compounds present in fruits and vegetables that is associated with cardio-protective effects is the flavanols [80] . Cocoa is also rich source of flavanols, a class of polyphenolic antioxidant compounds (e.g. (-)-epicatechin, (+)-catechin, procyanidins) found in plants [81] . In addition to their antioxidant activity, flavanols have also been associated with increased in nitric oxide bioavailability [82] [83] . Consumption of chocolate can result in significant increases in plasma epicatechin concentrations and decreases in plasma baseline oxidation products [84] . Since nitric oxide bioavailability deeply influences insulin-stimulated glucose uptake and vascular tone, flavanols have been evaluated for potential positive metabolic and pressor effects. Flavanoid-rich dark chocolate (100g) improved endothelial function and was associated with an increase in plasma epicatechin concentrations in healthy adults [85] [86] .

The effects of either dark or white chocolate bars on blood pressure and glucose and insulin responses to an oral-glucose-tolerance test in healthy subjects was compared [87] . After a 7-day cocoa-free run-in phase, 15 healthy subjects were randomly assigned to receive for 15 days either 100 g dark chocolate bars, which contained approximately 500 mg polyphenols, or 90 g white chocolate bars, which contained no polyphenols. Successively, subjects entered a further cocoa-free washout phase of 7 days, and then were crossed over to the other condition. Oral glucose tolerance tests were performed at the end of each period to calculate the homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI); blood pressure was measured daily. HOMA-IR was significantly lower after dark than after white chocolate ingestion (0.94 Â± 0.42 compared with

1.72 Â± 0.62; P < 0.001), and QUICKI was significantly higher after dark than after white chocolate ingestion (0.398 Â± 0.04 compared with 0.356 Â± 0.02; P = 0.001). Although within normal values, systolic blood pressure was lower after dark than after white chocolate ingestion (107.5 Â± 8.6 compared with 113.9 Â± 8.4 mm Hg; P < 0.05). These results suggest that dark but not white chocolate decreases blood pressure and improves insulin sensitivity in healthy persons.

These same researchers have also evaluated the effects of dark chocolate (DC) consumption on blood pressure (BP), flow-mediated dilation (FMD), oral glucose tolerance (OGTT), and insulin sensitivity in patients with essential hypertension (EH) [88] . After a 7-day chocolate-free run-in phase, 20 never-treated, grade I patients with EH (10 males; 43.7 Â± 7.8 years) were randomized to receive either 100 g per day DC (containing 88 mg flavanols) or 90 g per day flavanol-free white chocolate (WC) in an isocaloric manner for 15 days. After a second 7-day chocolate-free period, patients were crossed over to the other treatment. Noninvasive 24-hour ambulatory BP, FMD, OGTT, serum cholesterol, and markers of vascular inflammation were evaluated at the end of each treatment. The HOMA-IR, QUICKI, and insulin sensitivity index (SI) were calculated from OGTT values. Ambulatory BP decreased after DC (24-hour systolic BP -11.9 Â± 7.7 mm Hg, P < 0.0001; 24-hour diastolic BP -8.5 Â± 5.0 mm Hg, P < 0.0001), but not WC. DC but not WC decreased HOMA-IR (P < 0.0001), and it improved QUICKI, SI, and FMD. DC also decreased serum LDL cholesterol (from 3.4 Â± 0.5 to 3.0 Â± 0.6 mmol/L; P<0.05). In summary, DC decreased BP and serum LDL cholesterol, improved FMD, and enhanced insulin sensitivity in patients with EH. Additional studies in larger groups and in individuals with T2D will be needed to confirm these results.

BOTANICAL INTERVENTIONS

Botanicals have been used for medicinal purposes since the dawn of civilization [89] . It is well documented [90] that many pharmaceuticals commonly used today are structurally derived from natural compounds found in traditional medicinal plants. The development of the anti-hyperglycemic drug metformin (dimethlybiguanide; GlucophageÂ®) can be traced to the traditional use of Galega officinalis to treat diabetes, and the subsequent search to identify active compounds with reduced toxicity [91] [92] [93] . G. officinalis is far from the only botanical to have been used as a treatment for diabetes. Chinese medical books written as early as 3000 B.C. spoke of diabetes and described therapies for this disease [94] [95] . These historical accounts reveal that T2D existed long ago, and medicinal plants have been used for many millennia to treat this disease. To date, the anti-diabetic activities of well over 1200 traditional plants has been reported, although scant few have been subjected to rigorous scientific evaluation for safety and efficacy in humans [96] [97] [98] [99] [100] [101] . This section will provide a brief overview of those botanicals used for diabetes that have received the most scientific attention, have been evaluated for their anti-diabetic effects in individuals with diabetes, and are deserving of additional evaluation. The botanicals are presented in the order of their relative (highest-to-lowest) ranking for safety and efficacy.

Ipomoea batas (Caiapo)

Caiapo is derived from the skin of a variety of white sweet potato of South American origin, Ipomoea batatas, which is cultivated in a mountainous region in Kagawa Prefecture, Japan. It has been eaten raw for centuries in the belief that it is effective for anaemia, hypertension, and diabetes. Caiapo is commercially available throughout Japan without prescription, and used for the prevention and treatment of T2D. In rodents, caiapo exhibits anti-diabetic activity, and the active component is thought to be a high-molecular weight acid glycoprotein [102] [103] .

A beneficial effect of caiapo on glycemic control has been reported in several clinical studies. In a pilot study, a total of 18 male patients with T2D (age: 58 Â± 8 years; weight: 88 Â± 3 kg; BMI: 27.7 Â± 2.7 kg/m2; means Â± SEM) treated by diet alone were randomized to receive placebo (n = 6) or 2 (low dose; n = 6) or 4 g (high dose; n = 6) caiapo (four tablets each containing 168 or 336 mg powdered white-skinned sweet potato, respectively) before breakfast, lunch, and dinner for 6 weeks [104] . At the end of treatment, no statistically significant changes in fasting glucose, insulin, or lipids occurred in either the low-dose caiapo or placebo groups. In the group treated with the high dose caiapo, fasting plasma glucose (-13%) as well as cholesterol [total (-10.5%) and LDL (-13%) cholesterol] were significantly decreased (P < 0.05, compared to baseline). Body weight and blood pressure remained unchanged in all three groups. In patients receiving low-dose caiapo, insulin sensitivity (SI) increased by 37% (2.02 Â± 0.70 vs. 2.76 Â± 0.89 104 min-1 Â· Î¼U-1 Â· ml-1, P < 0.05); in those on high-dose caiapo, the FSIGT demonstrated an increase of SI by 42% (1.21 Â± 0.32 vs. 1.73 Â± 0.40 104 min-1 Â· Î¼U-1 Â· ml-1, P < 0.03). No changes were seen for SI in patients receiving placebo (1.52 Â± 0.28 vs. 1.35 Â± 0.21 104 min-1 Â· Î¼U-1 Â· ml-1). Glucose tolerance was significantly increased (~72%; P < 0.02) in the high-dose group [105] . No adverse events were reported.

The results of this pilot study have been confirmed in a randomized, double-blind placebo controlled trial [106] . A total of 61 patients with T2D treated by diet were given 4 g caiapo (n = 30; mean age 55.2 Â± 2.1 years; BMI 28.0 Â± 0.4 kg/m2) or placebo (n = 31; mean age 55.6 Â± 1.5 years; BMI 27.6 Â± 0.3 kg/m2) once daily for 12 weeks. Each subject underwent a 75-g oral glucose tolerance test (OGTT) at baseline and after 1, 2, and 3 months to assess 2-h glucose levels. Additionally, fasting blood glucose, HbA1C, total cholesterol, and triglyceride levels were measured. Fasting blood glucose levels decreased in the caiapo group (143.7 Â± 1.9 vs. 128.5 Â± 1.7 mg/dl; P < 0.001), and remained unchanged in the placebo group (144.3 Â± 1.9 vs. 138.2 Â± 2.1 mg/dl; P = 0.052). In the caiapo group, HbA1C decreased significantly (-0.53%; P < 0.001) from 7.21 Â± 0.15 to 6.68 Â± 0.14%, and remained unchanged in the placebo group (7.04 Â± 0.17 vs. 7.10 Â± 0.19%; P = 0.23). Two-hour glucose levels were significantly (P < 0.001) decreased in the caiapo group (193.3 Â± 10.4 vs. 162.8 Â± 8.2 mg/dl) compared with the placebo group (191.7 Â± 9.2 vs. 181.0 Â± 7.1 mg/dl). Mean cholesterol at the end of the treatment was significantly lower in the caiapo group (214.6 Â± 11.2 mg/dl) than in the placebo group (248.7 Â± 11.2 mg/dl; P < 0.05). A decrease in body weight was observed in both the placebo group (P = 0.0027), and in the caiapo group (P < 0.0001); in the caiapo group, body weight was related to the improvement in glucose control (r = 0.618; P < 0.0002). No significant changes in triglyceride levels or blood pressure were observed. Unfortunately, possible effects on fasting insulin, C-peptide, or insulin sensitivity were not reported in this study. Caiapo was well tolerated without significant adverse effects. This study confirms the results of the pilot with regard to the beneficial effects of caiapo on short-tem glycemic control (as well as cholesterol levels) and documents the efficacy of caiapo on long-term glycemic control in patients with T2D.

The magnitude of the effect of caiapo at reducing HbA1c (-0.53% absolute decrease) is comparable with that of Acarbose, an approved oral anti-hyperglycemic medication [107] , although it falls short of what has been suggested as the minimal acceptable level for a new anti-hyperglycemic medication (-0.7% absolute decrease) [108] . It will be of interest and important to see if the results of this very exciting outcome with caiapo can be confirmed in other well designed clinical trails, and to establish that caiapo does not exhibit any adverse interaction with existing anti-hyperglycemic medication.

Trigonella foenum-graecum (Fenugreek)

Trigonella foenum-graecum, also known as fenugreek, is an herb native to southeastern Europe, northern Africa, and western Asia, but is also widely cultivated in other parts of the world [109] . Fenugreek has a long history of traditional use in both Ayurvedic [holistic system of healing which originated among the Brahmin (Hindu priestly caste) sages of ancient India and Nepal approximately 3000 - 5000 years ago] and Chinese medicine [110] , and has been widely used for the treatment of diabetes [111] . The defatted seeds of the fenugreek plant contain ~50% fiber (similar to guar gum), along with a variety of bioactive saponins, alkaloids, coumarins, and 4-hydroxyisoleucine, the principle bioactive compound [112] [113] . This latter compound exhibits insulinotropic activity [114] [115] [116] ; following a 6-day sub-chronic administration, 4-hydroxyisoleucine (50 mg/kg/day) reduced fasting hyperglycemia, insulinemia, and improved glucose tolerance in diabetic rats [117] .

The clinical studies that have evaluated the efficacy of fenugreek in individuals with both type 1 and T2D have recently been reviewed [118] . In one study, 17 of 21 patients with T2D showed a reduction in 2-hour post-prandial glucose averaging 30 mg/dl following administration of 15 g of ground fenugreek seed [119] . In a crossover, placebo-controlled trial with 60 individuals with type 2 diabetes, the treatment group received 12.5 mg defatted fenugreek at lunch and dinner with isocaloric diets for 24 weeks [120] . Fasting blood glucose was 151 mg/dl at baseline, and reduced to 112 mg/dl after 24 weeks ($P < 0.05$). Fenugreek also caused a significant decrease in the area under the glucose curve by approximately 40%.

In a small study, the effects of fenugreek seeds on glycemic control and insulin resistance in mild-to-moderate T2D was performed using a double-blind, placebo-controlled design [121] . Twenty-five newly diagnosed patients with T2D (fasting glucose < 200 mg/dl) were randomly divided into two groups. Group I (n = 12) received 1 g/day of fenugreek seeds and Group II (n = 13) received standard care (dietary control, exercise) plus placebo capsules for two months. After two months, fasting blood glucose and two-hour post-glucose load blood glucose were not significantly different. However, following an oral glucose challenge, the area under the curve (AUC) for blood glucose (2375 Â± 574 vs 27597 Â± 274) and insulin (2492 Â± 2536 vs. 5631 Â± 2428) was significantly lower ($P < 0.001$), as was the HOMA-IR index (112.9 Â± 67 vs 92.2 Â± 57; $P < 0.05$) in the treatment group compared to control. Serum triglycerides were decreased and HDL cholesterol increased significantly (both $P < 0.05$) following fenugreek treatment. Significant reductions in total cholesterol and triglycerides have also been reported in other studies following fenugreek treatment [122] .

In an open label pilot study, fenugreek seeds were evaluated in combination with M. charantia and jamun seeds (Syzigium cumini) for effects on glycemic control in patients with T2D [123] . The patients were divided into two groups of 30 each. The patients of group I were given the raw powdered mixture in the form of capsules; the patients of group II were given this mixture in the form of salty biscuits. Daily supplementation of 1 g of this powered mixture for a 1.5-month period and increased to 2 g for another 1.5 months significantly reduced the fasting as well as the postprandial glucose level of the diabetic patients. A significant decrease in oral hypoglycemic drug intake and decline in percentage of the subjects who were on hypoglycemic drugs were found after the 3-month feeding trial. The authors concluded that 2 g of this powdered mixture of traditional medicinal plants in either raw or cooked form can be successfully used for lowering blood glucose in diabetics.

The doses of fenugreek used in clinical studies have ranged from 2.5 grams to 15 grams daily of the crushed and defatted seeds. Crushing is important in order to release the viscous gel fiber, which presumably contributes to the efficacy of fenugreek. Typical doses of seeds are in the range of 1-3 grams mixed with food and taken at mealtime. The most common side effects are gastrointestinal upset (diarrhea and flatulence), which often can be alleviated by dose-titration. Since the fenugreek fiber might absorb other oral medications, fenugreek should be taken independently (e.g. 1-2 h) of other medications. Due to its ability to lower blood glucose, individuals should monitor their glucose levels carefully if used in combination with insulin or other glucose-lowering agents. Fenugreek can exhibit anti-coagulant activity; it should not be used with other anti-coagulating agents due to the increased risk for bleeding.

The potential genotoxicity of a fenugreek seed extract (THL), containing a minimum of 40% 4-hydroxyisoleucine, was evaluated using the panel of assays recommended by US Food and Drug Administration for food ingredients (i.e. reverse mutation assay; mouse lymphoma forward mutation assay; mouse micronucleus assay). THL was determined not to be genotoxic under the conditions of the tested genetic toxicity battery [124] .

Cinnamomum cassia (Cinnamon)

Anderson and colleagues have previously reported that an ammonium hydroxide extract of cinnamon potentiated the effect of insulin on glucose oxidation in isolated rat adipocytes [125] [126] . Close evaluation of these in vitro data reveals that the cinnamon extract actually possessed insulin mimetic activity, since the stimulatory effects were independent of insulin concentration and no added insulin was required to achieve maximal glucose oxidation [127] . A water-soluble polyphenolic polymer from cinnamon has been isolated, and shown to have insulin-like activity as well as antioxidant activity in vitro [128] . Additionally, enzyme inhibition studies done have shown that the bioactive compound(s) isolated from cinnamon can stimulate autophosphorylation of a truncated form of the insulin receptor and can inhibit PTP-1, the rat homolog of the tyrosine phosphatase PTP-1B that inactivates the insulin receptor [129] [130] .

Three small studies have evaluated the use of cinnamon in T2D. The effects of cinnamon on blood glucose, triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol levels was evaluated in patients with T2D [131] . A total of 60 people with T2D (30 men and 30 women aged 52.2 Â± 6.32 years) were divided randomly into six groups. Groups 1, 2, and 3 consumed 1, 3,

or 6 g of cinnamon daily, respectively, and groups 4, 5, and 6 were given placebo capsules corresponding to the number of capsules consumed for the three levels of cinnamon. The cinnamon was consumed for 40 days, followed by a 20-day washout period. After 40 days, all three doses of cinnamon significantly reduced the mean fasting serum glucose (18-29%), triglyceride (23-30%), LDL cholesterol (7-27%), and total cholesterol (12-26%) levels; no significant changes were noted in the placebo groups. Changes in HDL cholesterol were not significant, and no significant adverse events were reported. The results of this interesting study suggest that intake of 1, 3, or 6 g of cinnamon per day reduces serum glucose, triglyceride, LDL cholesterol, and total cholesterol.

A more recent trial has evaluated an aqueous-purified cinnamon extract on long-term glycemic control and lipids in patients with T2D with equivocal results [132] . A total of 79 patients on insulin therapy but treated with oral anti-diabetics or diet were randomly assigned to take either cinnamon extract or a placebo capsule three times a day for 4 months in a double-blind study. The amount of aqueous cinnamon extract corresponded to 3 g of cinnamon powder per day. The mean absolute and percentage differences between the pre- and post-intervention fasting plasma glucose level of the cinnamon and placebo groups were significantly different. There was a significantly higher reduction in the cinnamon group (10.3%) than in the placebo group (3.4%). No significant intra-group or inter-group differences were observed regarding HbA1c, lipid profiles or differences between the pre- and post-intervention levels of these parameters The decrease in plasma glucose correlated significantly with the baseline concentrations, indicating that subjects with a higher initial plasma glucose level exhibited a greater response more from cinnamon intake [133] . No adverse effects were observed.

In a third study, a total of 25 postmenopausal patients with T2D (aged 62.9 Â± 1.5 y, BMI 30.4 Â± 0.9 kg/m2) participated in a 6-wk intervention, during which they were supplemented with either cinnamon (1.5 g/d) or a placebo [134] . Before and after 2 and 6 wk of supplementation, arterialized blood samples were obtained and oral glucose tolerance tests were performed. Blood lipid profiles and multiple indices of whole-body insulin sensitivity were determined. There were no time x treatment interactions for whole-body insulin sensitivity or oral glucose tolerance. The blood lipid profile of fasting subjects did not change after cinnamon supplementation. These results showed that cinnamon supplementation (1.5 g/d) did not improve whole-body insulin sensitivity or oral glucose tolerance, and did not modulate blood lipid profile in postmenopausal patients with T2D. Thus, the ability of cinnamon to improve long-term glycemic control has yet to be confirmed.

Mormordica charantia (Bitter melon)

Mormordica charantia is reported to be the most popular plant used worldwide to treat diabetes [135] [136] . It has many names depending on the geographic location of origin: in India, where it is widely used for diabetes [137] , M. charantia is known as karela, bitter melon, and bitter gourd. In other parts of the world, it is also known as wild cucumber, ampalaya, and cundeamor [138] . The glucose-lowering activity of M. charantia (administered as both fresh juice and unripe fruit) has been well documented in animal models of diabetes [139] [140] . Compounds possessing anti-diabetic activity include charantin and vicine [141] [142] [143] . In addition, other bioactive

components of bitter melon extract appear to have structural similarities to animal insulin (e.g. polypeptide-p) [144] [145] . Several modes of action have been proposed to account for the anti-diabetic activity of M. charantia including inhibition of glucose absorption in the gut, stimulation of insulin secretion, and the stimulation of hepatic glycogen synthesis [146] [147] . Four clinical trials have reported bitter melon juice, fruit, and dried powder to have a moderate hypoglycemic effect [148] [149] [150] . However, these studies were small and were not randomized or double-blind, and of insufficient quality to recommend the use of M. charantia without careful monitoring. When used at typical doses, 300-600 mg of juice extract or 1-2 g of powdered leaf daily, M. charantia is generally well tolerated, although it should not be used by children or pregnant women [151] [152] .

Gymnema sylvestre (Gurmar)

Gymnema sylvestre (also called gurmar), a woody plant that grows wild in India, has a long history of use in Ayurvedic medicine [153] . The leaves of G. sylvestre contain glycosides and the peptide gurmarin [154] [155] . Other plant constituents include resins, gymnemic acids, saponins, stigmasterol, quercitol, and several amino acid derivatives. A water-soluble acidic fraction called GS4 has been used in most clinical studies (see below). Several modes of action have been proposed to account for the anti-diabetic activity of G. sylvestre including increased glucose uptake and utilization, increased insulin secretion, and increased Î²-cell number [156] .

There have been several small clinical studies in individuals with type 1 and T2D (reviewed in [157]). These studies have reported that G. sylvestre decreases fasting glucose and HbA1c, lowered insulin requirements in individuals with type 1 diabetes, and lowered the dose of anti-hyperglycemic medications in individuals with T2D. G. sylvestre also appears to facilitate endogenous insulin secretion, but it is not a substitute for insulin. There are no data from double-blind, placebo-controlled studies in humans that validate the efficacy of G. sylvestre in type 1 or type 2 diabetes. The extract (~400 mg daily) of G. sylvestre is well tolerated, and no significant side effects have been reported.

Opuntia (fuliginosa, streptacantha) (Prickly pear cactus; Nopal)

Nopal, a member of the Opuntia genus, is widely used in Mexico as a treatment for glucose control [158] . It grows in arid regions throughout the Western hemisphere, and is know in the United States as prickly pear cactus. This plant produces both a vegetable, called nopal, and a red egg-shaped fruit called tuna. Nopal is a common component of every day foods including soups, salads, sandwiches, and blended in drinks. When used for glucose control, nopal is prepared as a food, and is available as in bulk, dried powder form or in capsules. The glucose-lowering activity of nopal is likely due to its very high soluble fiber and pectin content [159] [160] [161] , although its ability to reduce fasting glucose is suggestive of additional modes of action [162] .

The results of most human studies of this plant have been reported in Spanish-language journals [163] [164] ; two studies evaluating the acute effects of nopal have been published in English by Frati et al [165] [166] . Both studies used Opuntia streptacantha Lemaire, and reported improved glycemic control (decreased serum glucose) and improved insulin sensitivity (decreased serum insulin) following a single-dose (500 g of broiled or grilled nopal stems) in

patients with type 2 diabetes (n= 14 and n = 22). No effect was observed in healthy individuals [167], nor were any adverse effects reported. The potential clinical efficacy of this plant warrants further study.

Coccinia indica

Coccinia indica is a creeper plant (one that spreads by means of stems that creep) that grows wildly in Bangladesh and in many other parts of the Indian sub-continent. Although C. indica has a long history of use as an antidiabetic treatment in Ayurvedic medicine [168], it has not been subjected to the number of clinical trials that have evaluated M. charantia, fenugreek, or G. sylvestre (based on published reports). Neither the bioactive compounds nor mode of action C. indica have been well-characterized, but there is some suggestion that a component(s) of the plant possesses insulin-mimetic activity [169].

A double blind, placebo-controlled trial in which a preparation from the leaves of the plant was administered to patients with uncontrolled T2D for 6 weeks [170]. Of the 16 patients who received the experimental preparations, 10 showed significant improvement in their glucose tolerance ($P < 0.001$), while none out of the 16 patients in the placebo group showed improvement. Several other studies also offered supporting evidence of the beneficial effect of this treatment (reviewed in [171]). No adverse effects were reported. The potential clinical efficacy of this plant warrants further study.

Panax (ginseng, japoncicus, quinquefolius, eleutherococcus)

Ginseng, a member of the plant family Aaraliaceae, has been used in traditional Chinese medicine for thousands of years [172] [173] [174]. The botanical names for Asian ginseng (Chinese or Korean) is Panax ginseng; Japanese ginseng is known as Panax japonicus; American ginseng is Panax quinquefolius. Siberian ginseng belongs to the genus Eleutherococcus. Many therapeutic claims have been ascribed to the use of ginseng root extract including improved vitality and immune function, along with beneficial effects on cancer, diabetes, cardiovascular disease, and sexual function [175]. Bioactive compounds that have been identified in ginseng species include ginsenosides, polysaccharides, peptides, and fatty acids [176] [177]. Most pharmacological actions are attributed to the ginsenosides, a family of steroids named saponins [178] [179]. A comprehensive review of the randomized controlled trials (RCTs) evaluating ginseng extracts (mostly Panax ginseng and Panax quinquefolius) has been performed, and it was concluded by the authors that there was insufficient evidence to support efficacy for any of the above indications [180]. However, in light of the extreme compositional variability of ginsenoside concentrations reported in a sampling of 32 studies, it is possible that the anti-hyperglycemic efficacy might be as variable as its ginsenoside content [181] [182].

Two small studies have evaluated the use of ginseng in diabetes. In a double-blind, placebo controlled study, 36 patients with T2D were treated for 8 weeks with ginseng extract (species not specified) at 100 (n =12) or 200 (n = 12) mg/day, or with a placebo (n =12) [183]. Ginseng (100 and 200 mg/day) but not placebo lowered fasting blood glucose by approximately 0.5-1 mmol/l ($P < 0.05$). Eight subjects who were given ginseng and two who were given placebo

achieved normal fasting blood glucose. In response to an oral glucose challenge, the area under the 2-h blood glucose curve was reduced approximately 16% (P < 0.001) in the eight ginseng-treated patients who had normalized fasting blood glucose, without any concomitant change in immunoreactive insulin or C-peptide. The 200 mg dose improved HbA1c (~0.5% decrease; P < 0.05) and physical activity compared to placebo. Ginseng had no effect on plasma lipids. Another small study reported the acute effects of Panax quinquefolius administration (single dose on four separate occasions; 3 g/treatment) or placebo on glucose tolerance in patients with T2D (n = 9) and in non-diabetic subjects (n = 10) [184] . In both groups, ginseng caused a significant reduction (P < 0.05) in the area under the blood glucose curve by approximately 20% compared to placebo. The potential clinical efficacy of this plant warrants further study using a standardized extract.

Aloe vera

The dried sap of the aloe plant (aloes) is a traditional botanical remedy frequently used to treat dermatitis, burns and to enhance wound healing [185] , and one of a variety of plants used for diabetes in India [186] and the Arabian peninsula [187] . Its ability to lower the blood glucose was studied in 5 patients with type 2 diabetes [188] . Following the ingestion of aloe (one-half a teaspoonful daily for 4-14 weeks), fasting serum glucose level decreased in every patient from a mean of 273 Â± 25 (SE) to 151 Â± 23 mg/dl (P < 0.05) with no change in body weight. This glucose-lowering activity has been confirmed in two other studies which reported that oral administration of the aloes juice (1 tablespoon twice daily) reduced fasting glucose and triglycerides in subjects with type 2 diabetes both in the absence and presence of concomitant sulfonylurea therapy [189] [190] . No adverse effects were reported in these studies. Aloe gel also holds the potential for glucose-lowering activity, as it contains glucomannan, a water soluble fiber that reportedly has glucose-lowering and insulin sensitizing activities [191] [192] . The potential clinical efficacy of this plant warrants further study.

Allium (sativum and cepa) (Garlic)

Allium sativum (garlic) has been used as a medicinal herb by the ancient Sumarians, Egyptians, Greeks, Chinese, Indians, and later the Italians and English [193] . The leading Indian ancient medical text, Charaka-Samhita recommended garlic for the treatment of heart disease and arthritis for over many centuries [194] . Compounds present in aqueous garlic extract or raw garlic homogenate though to be the principle bioactive components include allicin (allyl 2-propenethiosulfonate or diallyl thiosulfonate), allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate, and Î³-L-glutamyl-S-alkyl-L-cysteine.

In modern times, garlic preparations have been widely recognized as agents for prevention and treatment of cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension and diabetes [195] [196] [197] . Epidemiological evidence indicates an inverse correlation between garlic consumption and the reduced risk of the development of cardiovascular disease [198] [199] [200] . The efficacy of garlic in cardiovascular diseases has been more evident in non-clinical models, thus prompting a variety of clinical trials [201] . Many of these trials have reported beneficial effects of garlic on almost all cardiovascular conditions

mentioned above [202] ; however, a number of studies have reported no beneficial effects, casting doubt on the reputed health benefits of garlic. These differences could have arisen as a result of methodological shortcomings, the use of different formulations/preparations of garlic, heterogeneity of patient populations, dietary inconsistencies, and different time scales of the studies. The glucose-lowering activity of garlic in humans with type 2 diabetes is not well studied. In the studies that have evaluated garlic, the data have been conflicting [203] [204] . Thus, the role of garlic in glucose control has yet to be confirmed.

Resveratrol

It has long been known that the French consume a much greater amount of saturated fats in their diet, yet suffer from a lower incidence of cardiovascular disease. This phenomenon has been termed â€˜The French Paradoxâ€™. It has been proposed that the greater amount of red wine consumed by the French protects them against the development of cardiovascular disease [205] [206] [207] . The intensive search for the actual molecule(s) that could be responsible for this almost miraculous activity led researchers to a compound identified as resveratrol. Resveratrol is a polyphenolic compound (a stillbenol) found in plants, especially red grapes and peanuts [208] . Red wine, produced from red grapes, contains the highest amount, on a percentage basis, of resveratrol ranging from 0.1 â€“ 14.3 mg per liter. The more resveratrol is investigated, the more its diverse health benefits emerge. In animals, resveratrol has been associated with anti-cancer activity, cardioprotective activity, antioxidant and glutathione-sparing activities, anti-inflammatory activity, anti-viral activity, and anti-neurodegenerative activity [209] [210] [211] . But without a doubt, the activities that affords resveratrol the most notoriety, is its ability to increase lifespan and delay age-related deterioration in a variety of experimental models [212] [213] . In experiments using yeast, nematodes (roundworms), fruit flies, and fish, resveratrol has been shown to increase mean lifespan by 18-70%, and maximum lifespan by 15-66%. While resveratrol has not yet been shown to increase lifespan in mammals, it has been consistently shown in mice to delay age-related diseases, improve metabolic efficiency, including a reduction in body weight and blood glucose, and largely mimic the biochemical and physiologic effects of caloric restriction, qualifying it, to a degree, as a caloric restriction mimetic [214] [215] .

What does resveratrol do at the mechanistic level that has led to its being the most widely recognized polyphenolic? The striking similarities of the benefits of caloric restriction and resveratrol led researchers to evaluate the effects of resveratrol on SIRT1 activation. These experiments have conclusively shown that resveratrol does, indeed, activate SIRT1 and its signaling partner, PGC -1a [216] [217] [218] . While there might be (and are) other important molecular targets of resveratrol including AMPK [219] , none are more important than SIRT1 and PGC -1a. In light of the critical roles played by SIRT1 and PGC -1a in mitochondrial biogenesis, the obvious question is what does resveratrol do, in this regard? Treatment of mice with resveratrol significantly increased their aerobic capacity, judged by their increased running time and oxygen consumption in their muscles [220] . Resveratrol induced the genes for oxidative phosphorylation and mitochondrial biogenesis, effects largely explained by the resveratrol-mediated decrease in PGC -1a acetylation and an increase in PGC -1a activity. This mechanism is consistent with resveratrol being a known activator of SIRT1, and by the lack of effect of resveratrol in cells lacking SIRT1. Importantly, resveratrol treatment protected mice

against diet-induced-obesity and insulin resistance [221] [222] [223] . If there was any doubt, these results obtained with resveratrol clearly implicate SIRT1 and PGC -1a as key regulators of energy and metabolic homeostasis. In fact, resveratrol and several related resveratrol analogs are now being developed as potential new therapies for type 2 diabetes [224] .

TRADITIONAL CHINESE MEDICINE

A discussion of botanical interventions for T2D would not be complete without the thoughtful consideration of Traditional Chinese Medicine. Over the centuries, Chinese herbal â€˜drugsâ€™ have served as a primary source for the prevention and treatment of many diseases including diabetes. Xiao-ke is a term used to refer to wasting and thirsting syndrome (T1D); the more modern term, Tang-niao-bing, means â€˜sugar urine illnessâ€™ (T2D) [225] . Unfortunately, a review of Traditional Chinese Medicine in the context of T2D is beyond the scope of this chapter. However, a number of excellent reviews on this subject are available, and will provide the reader with a more definitive evaluation of this subject than what could be accomplished in this presentation [226] [227] [228] [229] .

NON-BOTANICAL INTERVENTIONS

Oxidative stress, resulting primarily from chronic hyperglycemia, is a major cause of the complications of diabetes [230] . More recently, there is a growing appreciation of the role of oxidative stress as a mediator of insulin resistance and Î² dysfunction [231] [232] [233] . In this context, there are a growing number of studies in humans that have reported beneficial effects of antioxidants on various measures of abnormalities of diabetes [234] [235] [236] [237] . In addition, it is often reported that individuals with diabetes are deficient in one or more essential micronutrients, and that supplementation often provides a significant improvement. This section will provide a concise overview of those antioxidants, vitamins, minerals, and other dietary supplements (collectively referred to here as nutraceuticals) that have received the most attention as potential adjunct treatments for diabetes.

Antioxidants and Vitamins

Î±-Lipoic Acid

Î±-Lipoic acid (LA) is an eight-carbon fatty acid that is synthesized in trace quantities in organisms ranging from bacteria to man [238] [239] [240] . LA functions naturally as a cofactor in several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production [241] [242] . LA has been prescribed in Germany for over thirty years for the treatment of diabetes-induced neuropathy [243] [244] [245] . Results from several controlled clinical studies indicate that this compound is safe, well tolerated, and efficacious when administered intravenously [246] [247] [248] [249] . Results from a recently published study indicate that LA is equally efficacious at improving symptoms of diabetic neuropathy when administered orally [250] . New data obtained in animal models suggest that LA might be useful as an anti-obesity agent [251] . LA is commercially available in the US as a nutraceutical (dietary

supplement).

In addition to the beneficial effects of LA on diabetes-induced neuropathy, several clinical studies have reported an improvement in insulin sensitivity and whole-body glucose metabolism in patients with type 2 diabetes after continuous intravenous (iv) infusion of LA [252] [253] [254] [255]. Investigators have reported that a continuous infusion iv of LA substantially increases insulin-mediated glucose disposal (~30-50%) [256] [257]. Oral administration of LA (enteric-coated tablet) exerts a smaller (~20%) but nonetheless significant effect on insulin sensitivity [258] [259]. To overcome the abbreviated half-life of LA in plasma, a controlled release formulation of LA (CRLA) has been recently developed [260]. The pharmacokinetics, safety, and tolerability of CRLA were evaluated in healthy individuals and in patients with type 2 diabetes, and this agent was found to be safe, well-tolerated, and significantly reduced plasma fructosamine in patients with type 2 diabetes [261]. Also, non-controlled release LA recently has been reported to increase insulin mediated glucose disposal in patients with type 2 diabetes [262].

Although the exact mechanism of action of LA is unknown, in vitro data from the laboratories of Rudich and others have indicated that LA pretreatment maintains the intracellular level of reduced glutathione (the major intracellular antioxidant) in the presence of oxidative stress, and blocks the activation of serine kinases that could potentially mediate insulin resistance [263] [264] [265] [266]. Thus, one potential explanation for the protective effects of LA might be related to its ability to preserve the intracellular redox balance (acting either directly or through other endogenous antioxidants such as glutathione), thereby blocking the activation of inhibitory stress-sensitive serine kinases including IKKÎ² [267]. This stress-sensitive kinase is a crucial regulator of the transcription factor nuclear factor-ÎºB (NF-ÎºB), a major target of hyperglycemia, cytokines, reactive oxygen species, and oxidative stress [268] [269] [270]. The aberrant regulation of NF-ÎºB is associated with a number of chronic diseases including diabetes and atherosclerosis [271] [272]. The ability of LA to block the activation of NF-ÎºB is well established in vitro and in vivo [273] [274] [275] [276] [277].

Recent evidence has linked the activation of NF-ÎºB with insulin resistance [278] [279]. Activation of IKKÎ² inhibits insulin action. Salicylates, which inhibit IKKÎ² activity and block NF-ÎºB activation [280], restore insulin sensitivity both in vitro and in vivo [281] [282]. Treatment of nine patients with type 2 diabetes for two weeks with high-dose aspirin (7 g/day) resulted in a significant reduction in hepatic glucose production and fasting hyperglycemia, and increased insulin sensitivity [283]. The potential for toxicity associated with such a high dose of salicylate administered chronically precludes consideration of this agent for therapy, but the results support the rationale that IKKÎ² inhibition could be a useful pharmacological approach to increase insulin sensitivity. Furthermore, LA and other agents that interfere with the persistent activation of the NF-ÎºB pathway appear to be promising approaches to increase insulin sensitivity, and perhaps even as treatments for complications of diabetes in which NF-ÎºB activation has been implicated [284] [285].

L-Arginine

L-Arginine is classified as a â€˜semi-essentialâ€™ amino acid utilized by all cells [286] [287] [288]. It plays a critical role in cytoplasmic and nuclear protein synthesis, biosynthesis of other amino

acids and derivatives, and in the urea cycle. In this essential biochemical pathway, urea is synthesized from arginine to enable the body to remove excess ammonia, which is toxic to cells. L-arginine is classified a glucogenic amino acid because it can be metabolized into Î±-ketoglutarate, and enter the citric acid cycle (Krebâ€™s Cycle). In one of its most important roles, L-arginine serves as a direct precursor for the biosynthesis of NO [289] . Although this reaction was originally discovered to occur in endothelial cells, the generation of NO from L-arginine occurs in a variety of other cell types including skeletal muscle [290] [291] [292] . NO is produced endogenously from L-arginine in a complex reaction that is catalyzed by the enzyme nitric oxide synthase (NOS). The other product that is formed in this reaction is citrulline. NO serves as a second messenger to trigger blood vessel dilation and increase blood flow. L-arginine is the only physiological substrate that the NOS enzymes use as a nitrogen donor. Thus, under certain conditions, it may be rate limiting for NO production.

It is well established that aging leads to the deterioration of the vasculature and increased risk for cardiovascular disease [293] [294] [295] . Circulatory diseases account for considerable morbidity and almost half of all deaths in people over the age of 75 years. A major abnormality of the vasculature present in individuals with type 2 diabetes is endothelial dysfunction, or reduced blood flow capacity. As discussed above, NO is a major regulator of the blood flow. Basal release of NO from the vascular endothelium maintains a constant vasodilating tone. Impaired NO-mediated vasodilatation has been described in hypertension, diabetes, cardiovascular disease, and aging [296] [297] .

In atherosclerosis, the endothelium has a reduced capacity to produce NO and target cells are relatively insensitive to it [298] . The ability of NO to cause vasodilation provides an explanation for the mechanism of action of nitroglycerin, which has been used for over 100 years to treat patients with angina (pain due to inadequate blood flow to the heart) [299] . NO is produced following administration of nitroglycerin and other NO donors, such as L-arginine [300] [301] . In particular, L-arginine is a substrate for NOS, which is responsible for the endothelial production of NO.

Therefore, many investigators have evaluated the usefulness of L-arginine supplementation in animals and in humans in increasing NO production and improving cardiovascular health. The results of these studies have been summarized in several recent books [302] [303] and a review [304] . Results of oral L-arginine supplementation in hypercholesterolemic animals have consistently shown beneficial effects. L-arginine appears to inhibit the progression of atherosclerotic plaques and preserve endothelial function [305] . In addition, L-arginine affects other mediators of atherosclerosis, including circulating inflammatory cells and platelets [306] .

On balance, the data in humans have also been positive, although more variable [307] [308] [309] [310] [311] [312] [313] [314] [315] [316] [317] [318] . This variability is likely due to heterogeneous subject populations with a variety of non-standardized clinical symptoms, small sample sizes, abbreviated duration of treatment, and sub-therapeutic treatment doses. Five of the 17 studies showed no cardiovascular health benefit from oral L-arginine supplementation [319] . The remaining 12 studies demonstrated beneficial effects as evidenced by decreased platelet aggregation and adhesion, decreased monocyte adhesion, or improved endothelium-dependent vasodilation [320] . Taken together, these studies provide supporting evidence for the idea that

treatment with an exogenous NO donor could have a beneficial effect on cardiovascular health.

Vitamin C

Epidemiological evidence suggests that a high dietary intake of vitamin C, a marker of fruit and vegetable intake, is associated with a reduced risk for the development of cardiovascular disease [321] [322] . Plasma vitamin C, fruit intake, and dietary vitamin C intake is significantly and inversely associated with mean concentrations of C-reactive protein and tissue plasminogen activator (t-PA) antigen, a marker of endothelial dysfunction, suggesting that vitamin C has anti-inflammatory effects and is associated with lower endothelial dysfunction in men with no history of cardiovascular disease or diabetes [323] [324] . However, a high vitamin C intake from supplements has been reported to be associated with an increased risk of cardiovascular disease mortality in postmenopausal women with diabetes [325] .

The normal functions of vascular endothelial tissue include regulation of vasomotor tone, inhibition of platelet activity, and regulation of recruitment of inflammatory cells into the vasculature [326] . A damaged endothelium (â€˜endothelial dysfunctionâ€™) is a key event in the development of diabetic macroangiopathy, and is associated with the oxidative stress-mediated blunting of nitric oxide action [327] [328] [329] . Endothelial dysfunction has been documented in individuals who are insulin resistant, and in those at risk for developing T2D [330] [331] [332] .

The data as to whether vitamin C treatment (either acute or sub-chronic) exerts a beneficial effect on endothelial dysfunction in individuals with T2D is conflicting. Acute treatment with vitamin C improved endothelial function in obese subjects [333] , in patients with type 1 and T2D, and in women with gestational diabetes [334] [335] [336] .

In patients with cardiovascular disease including endothelial dysfunction, both acute (single dose, 2 g) and chronic treatment with vitamin C (30 days, 500 mg/d) reverses the vasomotor defect, as judged by increased flow-mediated dilation of the brachial artery [337] [338] . All of the above studies involved relatively small populations (< 75) and used acute treatment except one, which was for 30 days [339] . Nonetheless, the persistent finding of a beneficial effect of antioxidant treatment on endothelial function (flow-mediated dilation) in individuals with demonstrated endothelial dysfunction is encouraging. It is likely that these results will stimulate additional clinical studies of larger size and longer duration to evaluate the efficacy of vitamin C and perhaps other antioxidants.

In addition to playing a major role in the etiology of diabetic macroangiopathy, endothelial dysfunction could promote insulin resistance [340] . It is possible that oxidative stress-mediated blunting of nitric oxide action indirectly affects insulin sensitivity (e.g. reduced peripheral blood flow, increased peroxynitrite formation, others) consequently reducing insulin-stimulated glucose transport in skeletal muscle.

Cigarette smoking impairs endothelial function, and is one of the major risk factors for hypertension, atherosclerosis, and coronary heart disease. The effects of vitamin C (infusion) on insulin sensitivity and endothelial function (measured by flow-mediated dilation of brachial

artery; FMD) were evaluated in smokers, non-smokers with impaired glucose tolerance, and non-smokers with normal glucose tolerance [341] . Both insulin sensitivity and FMD were blunted in smokers and nonsmokers with IGT, compared with controls. In smokers and in non-smokers with impaired glucose tolerance, vitamin C significantly improved FMD, increased insulin sensitivity, and decreased plasma thiobarbituric acid-reactive substances, an index of oxidative stress. In contrast, vitamin C had no effect on these parameters in non-smokers with normal glucose tolerance. In patients with coronary spastic angina and endothelial dysfunction, vitamin C infusion augmented FMD and increased insulin sensitivity [342] . In contrast, vitamin C had no effect in healthy controls.

More recent studies have reported that vitamin C treatment significantly increased forearm vasodilatory response to reactive hyperemia only in patients with combined T2D and cardiovascular disease [343] , and improved endothelial dysfunction and attenuated post-prandiallipemia-induced oxidative stress in subjects with T2D [344] .

To test the hypothesis that the vitamin C influences microcirculatory function in patients with T2D, subjects were treated with 1 g of vitamin C three times a day for 2 weeks in a randomized placebo-controlled double-blind cross-over design. Microvascular reactivity was assessed by vital capillaroscopy and post-occlusive reactive hyperaemia. hs-CRP (high-sensitivity C-reactive protein), IL-6 (interleukin-6), IL-1ra (interleukin-1 receptor antagonist), and ox-LDL (oxidized low-density lipoprotein) were analyzed. The results showed no significant change in microvascular reactivity assessed after 2 weeks of vitamin C treatment. IL-1ra, IL-6, hs-CRP and ox-LDL did not change significantly, neither as absolute or relative values. In conclusion, in contrast with some studies reported previously, this study did not demonstrate an effect of continuous oral treatment with vitamin C on microvascular reactivity assessed at the level of individual capillaries, nor any indication of an effect on inflammatory cytokines or ox-LDL.

Using an excellent study design, the effects of high-dose oral vitamin C to alter endothelial dysfunction and insulin resistance in T2D was investigated [345] . Thirty-two diabetic subjects with low plasma vitamin C were enrolled in a randomized, double-blind, placebo-controlled study of vitamin C (800 mg/day for 4 wk). No significant changes in fasting glucose, insulin, SI (determined by glucose clamp), or forearm blood flow in response to ACh, SNP, or insulin were observed after vitamin C treatment. These results indicate that that high-dose oral vitamin C therapy, resulting in incomplete replenishment of vitamin C levels, is ineffective at improving endothelial dysfunction and insulin resistance in T2D.

Coenzyme Q10

Another antioxidant reported to have beneficial effects for diabetes is coenzyme Q10. Coenzyme Q is a vitamin-like molecule that has is frequently used in the treatment of several disorders primarily related to suboptimal cellular energy metabolism and oxidative stress [346] . The effects of orally administered coenzyme Q10 were evaluated in a double-blind, placebo-controlled study of 30 patients with coronary heart disease [347] . Following 8 weeks of treatment with coenzyme Q10 (60 mg twice daily), patients exhibited reduced plasma levels of glucose, insulin, (fasting and 2 hour), and lipid peroxides (a marker of oxidative stress) compared to controls. These results indicate that coenzyme Q10 decreased oxidative stress

and improved insulin sensitivity. Additional evaluation of coenzyme Q10 is clearly warranted.

To improve their lipid profiles, many patients with T2D are taking one of the HMG-CoA reductase inhibitors (i.e. statin class of drugs). Statins can reduce serum levels of coenzyme Q10 by up to 40% [348] [349] . The logical option is supplementation with coenzyme Q10 as a routine adjunct to any treatment that may reduce the endogenous production of coenzyme Q10, based on a balance of likely benefit against very small risk.

Vitamin E

Cardiovascular disease is the leading cause or morbidity and mortality in the Western world, and the major macrovascular complication of diabetes [350] . It is associated with increased oxidative stress [351] , and studies both in vitro and in vivo have provided the rationale for numerous prospective clinical studies evaluating the effects of vitamin E (Î±-tocopherol) on diabetes and cardiovascular events in different populations [352] [353] (see below). A review of these data by Jialal and colleagues has led to the overall conclusion that four of the five major prospective trials (data reported through 2001) have reported a beneficial effect on cardiovascular end-points, including cardiovascular death, nonfatal myocardial infraction, ischemic stroke, peripheral vascular disease, and others [354] . The one major study (HOPE Study [355]) that was negative for all end-points, had three limitations [356] . It was terminated early due to the overwhelming positive effects of the angiotensin-converting enzyme ramipril, it lacked data on the dietary intake of other antioxidants, and only evaluated synthetic vitamin E (a mixture of tocopherols and tocotrienols) and not Î±-tocopherol, the most potent and effective tocopherol.

In a study in patients with T2D evaluating the effects of vitamin E on biochemical risk factors for the development of cardiovascular disease, vitamin E treatment significantly reduced low-density lipoprotein oxidizability and soluble cell adhesion molecules [357] . Taken together, the evidence suggests a beneficial effect of vitamin E in patients with pre-existing cardiovascular disease, and in those who are at a greater risk for its development.

Oral vitamin E treatment appears to be effective in normalizing abnormalities in retinal hemodynamic, and improving renal function in patients with type 1 diabetes of short (disease) duration [358] . Vitamin E was beneficial in those individuals with poorest glycemic control and the most impaired retinal blood flow [359] . In a well-controlled study, short-term (4 weeks) supplementation of patients with T2D with persistent micro/macroalbuminuria with both vitamins E and C significantly lowered their urinary albumin excretion rate [360] . Four months treatment of patients with T2D with autonomic neuropathy with vitamin E improved the ratio of cardiac sympathetic to parasympathetic tone coincident with lowering of several indices of oxidative stress [361] . Interestingly, the study also reported a lowering of glycated hemoglobin, insulin, norepinephrine, and the homeoststatic model assessment index, indicative of increased insulin sensitivity and glycemic control. These data suggest that vitamin E and perhaps other antioxidant supplementation may provide a benefit in the treatment of microvascular complications of diabetes including diabetic retinopathy or nephropathy.

Initial reports of a positive effect of vitamin E on insulin action in insulin resistant patients with

T2D were published almost ten years ago [362] [363] . Twenty-five patients with T2D were treated with vitamin E (d-Î±-tocopherol; 900 mg/day) or placebo for three months in a double-blind, crossover design [364] . There was a trend in the reduction of plasma glucose, along with significant reductions in HbA1c levels (7.8 vs. 7.1), triglycerides, free fatty acids, total cholesterol, low-density lipoprotein cholesterol, and apoprotein B [365] . The Î² response to glucose was unaffected. These intriguing results prompted additional evaluations by Paolisso and colleagues using a more sensitive technique to measure insulin sensitivity, the euglycemic-hyperinsulinemic clamp.

Ten healthy subjects and 15 patients with T2D underwent an oral glucose tolerance test and euglycemic-hyperinsulinemic clamp before and after vitamin E supplementation (900 mg/d for 4 mo) [366] . In patients with T2D, vitamin E supplementation significantly increased both whole-body glucose disposal (i.e. insulin sensitivity) by approximately 50%, and non-oxidative glucose disposal by approximately 60%. Vitamin E also improved insulin action in the healthy subjects.

Vitamin E also improved insulin action in elderly people [367] . Twenty elderly, non-obese subjects with normal glucose tolerance were submitted to euglycemic-hyperinsulinemic clamp in a double-blind, crossover, and randomized study after 4 months treatment with either vitamin E (900 mg/d) or placebo. Whole-body glucose disposal was significantly potentiated by vitamin E compared to placebo. Furthermore, plasma vitamin E concentrations were correlated with net changes in insulin-stimulated whole-body glucose disposal.

In a 4-week, double-blind, randomized study of vitamin E administration (600 mg/d) versus placebo in 24 hypertensive patients, whole-body glucose disposal was measured by the euglycemic-hyperinsulinemic clamp [368] . In hypertensive subjects, vitamin E administration significantly increased whole-body glucose disposal, along with the ratio of reduced glutathione/oxidized glutathione in plasma. Four months treatment of patients with T2D with cardiac autonomic neuropathy with vitamin E lowered of glycated hemoglobin, insulin, norepinephrine, and the homeoststatic model assessment index, indicative of increased insulin sensitivity and improved glycemic control [369] .

The results from a large number of major intervention studies have all concluded that treatment with vitamin E is ineffective at improving glycemic control or endothelial function, altering the development of T2D, or at preventing cardiovascular disease [370] [371] [372] [373] [374] [375] [376] [377] ; some studies have even raised questions of its safety [378] [379] . In light of these results, the use of supplemental vitamin E (mixture or an individual isomer) for diabetes or cardiovascular health is no longer recommended.

Niacin

Niacin (nicotinic acid) has been used for many years to reduce elevated cholesterol and triglycerides. In addition, niacin has been shown to decrease cardiovascular events and mortality [380] . Some degree of angiographic regression has also being shown with niacin when used with other cholesterol medications. However, the use of niacin for the treatment of dyslipidemia-associated T2D has been limited, due to the adverse effect of high doses on glycemic control. Niacin is a B-vitamin (B-3), but when used in the doses necessary for blood

cholesterol control, it should be considered a drug and not a vitamin. Recently, it has been reported that niacin has the potential ability, when given in low doses, to be well tolerated and efficacious. In this study, treatment of individuals with dyslipidemia-associated T2D with extended-release niacin (Niaspanâ„¢) led to significantly improved lipid levels and minimal changes in glycemic control [381] . The extended-release form was designed to circumvent the bothersome side effects of regular niacin, such as flushing of the skin.

In this 16-week, double-blind, placebo-controlled trial, 148 patients were randomized to placebo (n = 49) or 1000 (n = 45) or 1500 milligrams per day (n = 52) of Niaspanâ„¢. About half of the study participants continued taking their prescribed statin drugs for cholesterol lowering during the trial, and 81 percent continued their medications for diabetes. Dose-dependent increases in high-density lipoprotein cholesterol levels (+19% to +24%; P < 0.05) vs. placebo for both niacin dosages) and reductions in triglyceride levels (-13% to -28%; P < 0.05) vs. placebo for the 1500-mg Niaspanâ„¢) were observed. Baseline and week 16 values for glycosylated hemoglobin levels were 7.13% and 7.11%, respectively, in the placebo group; 7.28% and 7.35%, respectively, in the 1000-mg Niaspanâ„¢ group (P < 0.16 vs. placebo); and 7.2% and 7.5%, respectively, in the 1500-mg Niaspanâ„¢ group (P < 0.048 vs placebo). Four patients discontinued participation because of inadequate glucose control. Rates of adverse event rates other than flushing were similar for the niacin and placebo groups. Four patients discontinued participation owing to flushing (including 1 receiving placebo). No hepatotoxic effects or myopathy were observed. The authors concluded that low doses of Niaspanâ„¢ (1000 or 1500 mg/d) are a treatment option for dyslipidemia in patients with T2D.

Patients with diabetic dyslipidemia are commonly treated with triglyceride-lowering fibrate drugs, but niacin appears more effective than the fibrates for raising HDL. Since most patients with diabetes will require lipid-lowering therapy, the use of statins to lower LDL cholesterol has become routine therapy for the majority of patients. This study suggests that the addition of extended release low-dose niacin to statin therapy could provide an additional benefit for improvement of blood lipids and lipoproteins in patients with diabetes. However, the impact of niacin on glycemic control will still require regular monitoring.

Minerals and Trace Elements

Chromium

Second only to calcium, chromium is very popular mineral supplement in the US, with over 10 million individual users; in 2005, retail sales of chromium picolinate-containing products totaled over $130 million, and represent approximately 20% of the total market for chromium-containing products. Several authors, mostly on the basis of small studies of short duration, have suggested dietary trivalent chromium supplementation as an attractive option for the management of T2D and for glycemic control in persons at high risk for T2D [382] [383] . Thus, chromium has emerged as the most widely used dietary supplement for the treatment of T2D in the US. The link between chromium and carbohydrate metabolism was proposed over 40 years ago, when it was identified as a component of the biologically active â€˜glucose tolerance factorâ€™ [384] . Chromium deficiency has been associated with decreased insulin action in

both diabetic animals and humans [385] [386] [387] . Some but not all human studies have found that chromium supplementation has beneficial effects in individuals with impaired glucose tolerance and diabetes [388] [389] [390] [391] [392] . Oral administration of trivalent chromium is associated with favorable safety profile in animals and in humans [393] [394] .

To critically evaluate the clinical studies with chromium-treatment reported to date, a systematic review and meta-analysis of the RCTs were performed [395] . The objective was to determine the effect of chromium on glucose and insulin responses in healthy subjects and in individuals with glucose intolerance or T2D. The authors identified 20 reports of RCTs assessing the effects of chromium on glucose, insulin, or HbA1c. Their analyses summarized data on 618 participants from the 15 trials that reported adequate data: 193 participants had T2D and 425 were in good health or had impaired glucose tolerance. The meta-analysis showed no association between chromium and glucose or insulin concentrations among non-diabetic subjects. A study of 155 diabetic subjects in China reported that chromium reduced glucose and insulin concentrations [396] ; the combined data from the 38 diabetic subjects in the other studies did not. Three trials reported data on HbA1c: one study each of persons with T2D [397] , persons with impaired glucose tolerance [398] , and healthy subjects [399] . The study of diabetic subjects in China was the only one to report that chromium significantly reduced HbA1c [400] . Thus, this meta-analysis of RCTs showed no effect of chromium on glucose or insulin concentrations in non-diabetic subjects, and data for persons with diabetes are inconclusive.

More recent reports suggest that the ability of chromium to improve glycemic control and/or increase insulin sensitivity is better observed in subjects with glucose intolerance, insulin resistance, type 1 diabetes, T2D, or gestational diabetes, rather than in healthy normal subjects [401] . Furthermore, these studies suggest that the form of chromium influences the study results, and that the picolinate form provides greater efficacy [402] . Absorption and bioavailability studies of the various forms of commercially available chromium have shown that chromium picolinate is more readily absorbed and is more bioavailable than the other forms of chromium that have been clinically tested in subjects with diabetes [403] [404] . This may account for some of the disparity seen in the glycemic response observed in the clinical studies conducted to date.

In contrast to the results reported by others [405] [406] , a recent study has found that chromium picolinate (500 and 1000 Î¼g daily for 6 months) was ineffective at reducing HbA1c in obese, poorly-controlled, insulin-dependent individuals with T2D [407] . Possibilities to explain this contrasting result are the limited statistical power to detect a significant change due to the small number of subjects (n = 17 for placebo group; n = 14 for 500 Î¼g group; n = 15 for 1000 Î¼g group), greater degree of obesity (and insulin resistance) at baseline (BMI = 33-35 kg/m2), and the severity of diabetes control at baseline (HbA1c = 9.4-9.7%). Furthermore, these subjects were unable to achieve adequate glycemic control even with anti-hyperglycemic medication, and required a very high dose of insulin.

Although the exact mechanism of chromium action has not been definitively established, data from a recent in vivo study suggest that chromium might exhibit its insulin sensitizing effect by reducing the content and activity of the tyrosine phosphatase PTP-1B [408] . PTP-1B has long been implicated in the regulation of insulin receptor tyrosine phosphorylation and tyrosine

kinase activity [409] , and has been validated as a bona fide pharmacological target for increasing insulin sensitivity [410] [411] [412] [413] [414] . In animals, small molecules that inhibit PTP-1B increase insulin sensitivity and lower plasma glucose [415] [416] [417] . Alternatively, chromium might act directly on the insulin receptor, and increase its tyrosine kinase activity [418] , as has been observed with other small molecules [419] [420] .

Additional RCTs in well-characterized, at-risk populations are necessary to determine the effects of chromium on glucose, insulin, and HbA1c. To this end, the Office of Dietary Supplements (ODS), the National Center for Complementary and Alternative Medicine (NCCAM), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invited basic and clinical applications to study the role of chromium as adjuvant therapy in T2D and/or impaired glucose tolerance (http://grants1.nih.gov/grants/guide/pa-files/PA-01-114.html ; program announcement expired 10/1/2004).

Magnesium

Magnesium, the fourth most abundant cation in humans, is an essential mineral in human nutrition, and is required for wide array of biological functions [421] [422] . It is a cofactor in over 300 enzymatic reactions, and is important for the electrical stability of cells, maintenance of membrane integrity, muscle contraction, nerve conduction and vascular tone. Magnesium deficiency is linked to a number of clinical disorders including insulin resistance, T2D, hypertension, and cardiovascular disease [423] [424] [425] [426] [427] [428] [429] [430] . Epidemiological studies strongly indicate that high daily magnesium intake is predictive of a lower risk for T2D in both men and women [431] [432] [433] [434] . The plasma magnesium level is inversely related to insulin sensitivity in adults [435] [436] [437] and obese children [438] , and parenteral magnesium supplementation improves insulin sensitivity as well as insulin secretion in patients with T2D [439] [440] [441] . However, until recently (see below), no beneficial effect of oral magnesium supplementation has been demonstrated on glycemic control either in patients with type 1 or T2D. Nonetheless, RCTs in well-characterized, at-risk populations are warranted to see whether magnesium replacement therapy will prove efficacious in the treatment of T2D.

To this end, it has recently been reported that oral magnesium supplementation (as a solution of magnesium chloride, MgCl22) restores serum magnesium levels, and improves insulin sensitivity and metabolic control in patients with T2D [442] . This study was a randomized double-blind placebo-controlled design, in which 63 subjects with decreased serum magnesium (â‰¤ 0.74 mmol/l) treated by glibenclamide received either 50 ml of MgCl2 solution (50 g/l) or placebo daily for 16 weeks. At the end of the study, MgCl2-treated subjects showed a significantly higher serum magnesium concentration (0.74 Â± 0.10 vs. 0.65 Â± 0.07 mmol/l, P < 0.02) and lower HOMA-IR index (3.8 Â± 1.1 vs. 5.0 Â± 1.3, P < 0.005), fasting glucose levels (8.0 Â± 2.4 vs. 10.3 Â± 2.1 mmol/l, P < 0.01), and HbA1c (8.0 Â± 2.4 vs. 10.1 Â± 3.3%, P < 0.04) compared to placebo-treated subjects.

Subsequently, in a smaller pilot study (n = 9), the effects of magnesium (Mg) supplementation on patients with T2D with stable glycemic control were investigated [443] . Water from a salt lake with a high natural Mg content (7.1%) (MAG21) was used for supplementation after dilution with distilled water to 100mg/100mL; 300mL/day was given for 30 days. Fasting serum

immunoreactive insulin level decreased significantly, as did HOMA-IR (both P < 0.05). There was also a marked decrease of the mean triglyceride level after supplementation. The patients with hypertension showed significant reduction of systolic (P < 0.01), diastolic (P = 0.0038), and mean (P < 0.01) blood pressure. Taken together, these results support the use of oral magnesium supplementation in patients with T2D who are magnesium-depleted.

Zinc

Zinc is another essential mineral in human nutrition with a wide range of biological functions. Zinc fulfills catalytic, structural, or regulatory roles in more than 200 zinc-requiring metalloenzymes [444] . The interaction of zinc with insulin induces conformational changes and enhances binding to the insulin receptor [445] [446] . Zinc ions possess insulin mimetic activity, perhaps through their ability to inhibit protein tyrosine phosphatases, including PTP-1B [447] . With regard to glucose metabolism, zinc is a co-factor of several key enzymes. Zinc is an activator of fructose-1-6-bisphosphate aldolase, and an inhibitor of fructose-1-6-biphosphatase [448] . Zinc can also exert antioxidant activity [449] , and is a cofactor in copper/zinc superoxide dismutase, a major antioxidant enzyme [450] .

Some studies have reported zinc deficiency along with alterations in zinc metabolism in patients with diabetes [451] [452] [453] [454] . Zinc supplementation studies in patients with diabetes are few, and have yielded contradictory results with regard to effects on glycemic control [455] [456] . Interestingly, a recent study has confirmed previous reports that diabetic patients (both Type 1 and T2D) have significantly lower mean serum zinc levels compared with healthy controls [457] , and that zinc supplementation (30 mg/day for 12 weeks) in the patients with T2D elevated their serum zinc level and significantly decreased HbA1c. In a 12-week randomized, double-blind placebo controlled study (n =18 per group) designed to evaluate the effects vitamin/mineral combination therapy on indices of nephropathy in patients with T2D, zinc (30 mg /day), when used in combination with magnesium (200 mg/day), vitamin C (200 mg), and vitamin E (100 IU/day) decreased the level of urinary albumin excretion (P = 0.005, respectively), without affecting urinary N-acetyl-beta-d-glucosaminidase activity [458] . The combination also resulted in a significant decrease in fasting serum glucose (P = 0.035) and malondialdehyde (P = 0.004) [459] , along with an increase in HDL cholesterol and apolipoprotein A1 levels (P = 0.019) [460] . These results provide evidence for the beneficial effects of combination of magnesium, zinc, and vitamins C and E supplementation on improving glomerular (but not tubular) renal function in type 2 diabetic patients, and on metabolic control.

Vanadium

Vanadium is a transition metal that can exist in several oxidation states (-1 to +5), and is widely present in nature in the form of minerals [461] . It is also found in animals and humans, primarily as the tetravalent vanadyl cation (VO2+) and the pentavalent vanadate (VO3-). The tetravalent form is the most common intracellular form whereas the pentavalent form predominates in extracellular body fluids. Animals fed vanadium-deficient diets exhibited an increased rate of spontaneous abortion, depressed milk production, decreased growth, and premature death. The nutritional necessity in humans has not been established. The â€˜averageâ€™ diet in the US supplies approximately 15-60 micrograms of vanadium daily. Foods relatively rich in vanadium

include black pepper, mushrooms, shellfish, parsley, and dill seed. Fresh fruits, vegetables, and oils contain little or no vanadium.

In vitro and in vivo, vanadium-containing compounds exhibit insulin-mimetic activity primarily due to their ability to inhibit tyrosine phosphatase activity [462] [463] [464] [465] and activate a cytosolic tyrosine kinase [466]. Many of the metabolic effects of insulin including the stimulation of glucose transport, glycogen synthesis, glucose oxidation, and lipogenesis and anti-lipolysis are mimicked by vanadate and related peroxovanadium compounds [467] [468] [469]. In vivo, vanadate and peroxovanadium compounds significantly lower blood glucose in insulin-dependent and insulin-resistant diabetic animals in the absence of overt toxicity [470] [471] [472] [473] [474]. The glucose-lowering effect of vanadate is achieved without elevating serum insulin, indicating an insulinomimetic effect and, in some cases, an insulin sensitizing effect.

In humans with T2D, several small studies of 2-4 weeks duration have indicated small but significant beneficial effects of vanadate treatment on various indicators of glucose metabolism [475] [476] [477] [478] [479] [480]. The most common side effects were gastrointestinal disturbances: nausea, vomiting, diarrhea, and cramps. In the study from Cusi et al [481], eleven patients with T2D were treated with vanadyl sulfate (VS) at a higher dose (150 mg/day) and for a longer period of time (6 weeks) than in the previous studies. Before and after treatment insulin secretion during an oral glucose tolerance test, and hepatic glucose production (HGP) along with whole body insulin-mediated glucose disposal were measured. Treatment significantly improved glycemic control: fasting plasma glucose (FPG) decreased from 194 Â± 16 to 155 Â± 15 mg/dl, fructosamine decreased from 348 Â± 26 to 293 Â± 12 Î¼mol/l, and HbA1C decreased from 8.1 Â± 0.4 to 7.6 Â± 0.4% (all P < 0.01) without any change in body weight. Subjects had an increased rate of HGP compared with non-diabetic controls (4.1 Â± 0.2 vs. 2.7 Â± 0.2 mg/kg lean body mass/min; P < 0.001), which was closely correlated with FPG (r = 0.56; P < 0.006). Vanadyl sulfate reduced HGP by about 20% (P < 0.01), and the decline in HGP was correlated with the reduction in FPG (r = 0.60; P < 0.05). VS also caused a modest increase in insulin-mediated glucose disposal (from 4.3 Â± 0.4 to 5.1 Â± 0.6 mg/kg lean body mass/min; P < 0.03), although the improvement in insulin sensitivity did not correlate with the decline in FPG after treatment (r = -0.16; P = NS). Thus, VS at a dose of 150 mg/day for 6 weeks improves hepatic and muscle insulin sensitivity in patients with T2D. The glucose-lowering effect of VS correlated well with the reduction in HGP, but not with insulin-mediated glucose disposal, suggesting that liver, rather than muscle, is the primary target of VS action at therapeutic doses.

Vanadium has a poor therapeutic index, and attempts have been made to reduce the dose of vanadium required for therapeutic effectiveness [482]. Organic forms of vanadium, as opposed to the inorganic VS, are appear to be safer (in animal studies), more absorbable, and able to deliver a therapeutic effect up to 50% greater than the inorganic forms [483] [484]. An ongoing goal has been to provide vanadium with increased bioavailability, and in a form that is best able to produce the desired biological effects [485] [486]. As a result, numerous organic complexes of vanadium have been developed including bis(maltolato)oxovanadium (BMOV), bis(cysteinamide N-octyl)oxovanadium known as Naglivan, bis(pyrrolidine-N-carbodithioato)oxovanadium, vanadyl-cysteine methyl ester, and bis-glycinato oxovanadium (BGOV) [487] [488] [489]. Other forms of vanadium, including polyoxovanadium [490] and vanadylpicolinate complexes [491] have also been proposed. The usefulness of these newer formulations as clinical agents for T2D

remains to be determined. Despite the encouraging results of the clinical studies published to date, the safety of larger doses and use of vanadium salts (or related compounds) for longer periods is unknown [492] . Thus, the use of supplemental vanadium for the management of diabetes or impaired glucose tolerance is not recommended at this time.

Fatty Acids

Polyunsaturated Fatty Acids

Dietary Ï‰-3 polyunsaturated fatty acids (Ï‰-3 PUFAs) exhibit a broad array of biological activities in health and disease, including anti-inflammatory, lipid-lowering, and the prevention of coronary heart disease [493] [494] [495] [496] [497] [498] . The most prominent dietary sources of Ï‰-3 PUFAs include fish oils abundant in eicosapentanoic (EPA) and docosahexanoic (DHA) acids along with plants rich in Î±-linolenic acid. A primary mechanism of action of Ï‰-3 PUFAs is achieved by altering gene expression mediated by the regulation of the activities or abundance of four families of transcription factors [499] [500] [501] [502] . These include the peroxisome proliferator activated receptor (PPAR Î±,Î³,Î´), liver X receptors (Î±,Î²), hepatic nuclear factor-4 Î±, and the sterol regulatory element binding proteins 1 and 2. These transcription factors play major roles in the regulation of hepatic carbohydrate, fatty acid, triglyceride, cholesterol and bile acid metabolism.

A large body of epidemiological and clinical trial data suggests that Ï‰-3 PUFAs play a significant role in the prevention of coronary artery disease [503] [504] [505] . The most convincing evidence is derived from four major intervention trials evaluating either fish meal, fish oil, or an Î±-linolenic acid-enriched spread on hard clinical end-points including myocardial infarction, death from coronary heart disease, and total mortality [506] [507] [508] [509] . In essence, these studies found that supplementation significantly reduced cardiovascular events (cardiovascular death, non-fatal myocardial infarction and stoke) [510] [511] [512] and total mortality [513] . The average recommended intake by an expert panel of US nutritional scientists is 2.2 g/d of Î±-linolenic acid and 0.65 g/d of EPA plus DHA [514] , while the British Nutrition Foundation has recommended 2.4 g/d of Î±-linolenic acid and 1.2 g/d of EPA plus DHA [515] .

An interim report from The Japan EPA Lipid Intervention Study (JELIS) was presented at the American Heart Association Meeting in November 2005 (http://www.americanheart.org/presenter.jhtml?identifier=3035468) [516]). Of 18,645 eligible participants, 9,326 were given 1,800 milligrams (mg)/day of highly purified EPA capsules as add-on therapy to a statin. The primary endpoint of the study was experiencing any one of a group of outcomes that included sudden cardiac death, heart attack, unstable angina (sustained chest pain due to the heartâ€™s oxygen starvation), or undergoing procedures to reopen blocked arteries, such as angioplasty/stenting or coronary artery bypass surgery. After more than 4.5 years of follow-up, the primary endpoint was seen in 2.8 percent of patients treated with statins plus EPA compared to 3.5 percent in the statin-only group, represents an approximate 20 percent reduction in risk EPA plus statin treatment compared to statin treatment alone.

Conflicting results have been reported regarding the effects of fish oil supplementation on

glycemic control in those with glucose intolerance including individuals with T2D. Several early studies reported detrimental effects [517] [518], but subsequent studies with improved design have not replicated the earlier findings [519] [520] [521] [522]. Results from a meta-analysis of pooled data from all RCTs in which fish oil supplementation was the only intervention in subjects with T2D was recently published [523]. Eighteen trials including 823 subjects followed for a mean of 12 weeks were included. Doses of fish oil used ranged from 3 to 18 g/day. The outcomes studied were glycemic control and lipid levels. Meta-analysis demonstrated a statistically significant effect of fish oil on lowering triglycerides (-0.56 mmol/l) and raising LDL cholesterol (0.21 mmol/). No statistically significant effect was observed for fasting glucose, HbA1c, total cholesterol, or HDL cholesterol. The triglyceride-lowering effect and the elevation in LDL cholesterol were most evident in those trials that recruited hypertriglyceridemic subjects and used higher doses of fish oil. Thus, this meta-analysis of RCTs showed that fish oil supplementation in T2D lowers triglycerides, raises LDL cholesterol, and has no statistically significant effect on glycemic control. There is no evidence that fish oil supplementation adversely effects glucose tolerance, insulin action, or insulin secretion in non-diabetic individuals [524]. There is some evidence that fish oil may improves defects in insulin action and prevent alterations in glucose homeostasis and the further development of T2D [525].

A recent report has shown that, in individuals with T2D but without hypertriglyceridemia, fish oil supplementation for 9 weeks moderately increased blood glucose and decreases insulin sensitivity [526].

Conjugated Linoleic Acid (CLA)

Conjugated linoleic acid (CLA) refers to a group of polyunsaturated fatty acids that are positional and geometric conjugated dieonic isomers of linoleic acid [527]. The biological activity of CLA was originally discovered due to its ability to inhibit chemically induced carcinogenesis in rodents [528] [529]. Subsequently, numerous health benefits have been attributed to CLA including activity as an anti-obesogenic, anti-diabetogenic, and anti-atherosclerortic agent [530] [531]. The major isomers of CLA are the cis-9,trans-11 and the trans-10, cis-12, with their biological activities being isomer-specific [532]. The major dietary sources of CLA are meat and dairy products. CLA concentrations in dairy products typically range from 2.8 to 7.0 mg/g fat (frozen yogurt and condensed milk, respectively), of which the cis-9,trans-11 isomer comprises ~75%-95% of the total CLA [533]. CLA concentrations in meat typically range from 0.6 to 5.8 mg/g fat (pork and lamb, respectively), of which the cis-9,trans-11 isomer comprises ~55%-85% of the total CLA [534]. Similar to Ï‰-3 PUFAs, CLA isomers are ligands and activators of PPARÎ±, but with an approximate 10-fold higher affinity (~140-260 nM) [535]. CLA isomers readily undergo extensive metabolism including elongation and desaturation, yielding additional potential bioactive molecules [536].

In several animal models, CLA has been shown to reduce body fat accumulation, improve glucose tolerance, and increase insulin sensitivity [537] [538]. In individuals with T2D (n =12), plasma trans-10, cis-12 but not cis-9,trans-11 CLA is inversely correlated with body weight ($P < 0.05$) and serum leptin ($P < 0.02$) [539]. Thus, CLA supplementation has been suggested as a potential new nutraceutical approach for obesity, a major risk factor for the development of T2D. However, conflicting results have been reported regarding the beneficial effects of CLA

supplementation on adiposity and metabolism in humans [540] [541] [542] [543] . In several studies, administration of CLA (1.8-4.2 g/day) for 12 weeks has been reported to decrease body fat mass (~4%; P < 0.001) in healthy individuals [544] [545] and in overweight and obese individuals [546] . There were no changes in body weight, serum lipids, or glucose metabolism in these studies.

However, in another study, abdominally obese men (n = 60) were treated with 3.4 g/day CLA (isomer mixture), purified trans-10, cis-12 CLA, or placebo [547] . Euglycemic-hyperinsulinemic clamp, serum hormones, lipids, and anthropometry were assessed before and after 12 weeks of treatment. Baseline metabolic status was similar between groups. Unexpectedly, trans-10, cis-12 CLA increased insulin resistance (19%; P < 0.01) and glycemia (4%; P < 0.001) and reduced HDL cholesterol (-4%; P < 0.01) compared with placebo. Body fat, sagittal abdominal diameter, and weight decreased versus baseline, but the difference was not significantly different from placebo. The CLA mixture did not change glucose metabolism, body composition, or weight compared with placebo but lowered HDL cholesterol (-2%; P < 0.05). Trans-10, cis-12 CLA also increases markers of oxidative stress and inflammation [548] , thus revealing important isomer-specific metabolic actions of CLA in abdominally obese men.

The detrimental effect of the CLA mixture on insulin sensitivity was confirmed by another group. The effect of CLA supplementation on markers of glucose and insulin metabolism, lipoprotein metabolism, and inflammatory markers of CVD in subjects with T2D [549] . The study was a randomized, double-blind, placebo-controlled trial. Thirty-two subjects with stable, diet-controlled type 2 diabetes received CLA (3.0 g/d; 50:50 blend of cis-9, trans-11 CLA and trans-10, cis-12 CLA) or control for 8 wk. A 3-h 75-g oral-glucose-tolerance test was performed, and fasting plasma lipid concentrations and inflammatory markers were measured before and after the intervention. CLA supplementation significantly increased fasting glucose concentrations (6.3%; P < 0.05) and reduced insulin sensitivity as measured by homeostasis model assessment, oral glucose insulin sensitivity, and the insulin sensitivity index (composite) (P = 0.05). Total HDL-cholesterol concentrations increased by 8% (P < 0.05), which was due to a significant increase in HDL(2)-cholesterol concentrations (P < 0.05). The ratio of LDL to HDL cholesterol was significantly reduced (P < 0.01). CLA supplementation reduced fibrinogen concentrations (P < 0.01), but had no effect on inflammatory markers of CVD. Thus, supplementation with a CLA mixture had an adverse effect on insulin and glucose metabolism.

The effects of trans-10, cis-12 CLA supplementation on plasma proinsulin, insulin, C-peptide and adiponectin concentrations, including their associations with change in insulin sensitivity, has also been evaluated [550] . The study was a randomized, double-blind, placebo-controlled trial. Fifty-seven non-diabetic abdominally obese men received either 3.4 g trans-10, cis-12 CLA, CLA-isomer mixture, or control oil for 12 weeks. Insulin sensitivity (hyperinsulinemic-euglycemic clamp), intact proinsulin, insulin, the proinsulin : insulin ratio, C-peptide, glucose, and adiponectin were assessed before and after supplementation. Supplementation with trans-10, cis-12 CLA increased proinsulin (P < 0.01), the proinsulin : insulin ratio (P < 0.05) and C-peptide concentrations (P < 0.001) in comparison with control subjects. Adiponectin did not change significantly. The change in proinsulin, but not the proinsulin : insulin ratio, was related to impaired insulin sensitivity (r = -0.58; P <0.0001), independently of changes in insulin, C-peptide, glucose, adiponectin and BMI. Thus, in obese, non-diabetic men, trans-10, cis-12 CLA

induced hyperproinsulinemia that was related to impaired insulin sensitivity, independently of changes in insulin concentrations. These results are of clinical interest, as hyperproinsulinemia predicts diabetes and cardiovascular disease. In light of these results, the use of supplemental CLA (mixture or an individual isomer) for the management of obesity, impaired glucose tolerance, or diabetes is definitely not recommended.

SUMMARY AND POSSIBILITIES FOR TREATMENT

Clearly, many natural products including botanicals and other nutraceuticals have hypoglycemic, anti-hyperglycemic, insulin sensitizing, anti-hyperlipidemic, anti-hypertensive, and anti-inflammatory activities. There are published studies reporting the anti-diabetic activity of well-over a thousand different botanicals and nutraceuticals. The number of those treatments evaluated in clinical trials is approximately 100 [551] . In the vast major of these trials, the botanicals and nutraceuticals were evaluated as an adjunct to diet and prescription medications. Fifty-eight of the trials were controlled, and conducted in individuals with diabetes or impaired glucose tolerance. Of these, statistically significant treatment effects were reported in 88% of trials (23 of 26) evaluating a single botanical, and 67% of trials (18 of 27) evaluating individual vitamin or mineral supplements (reviewed in [552]). When reported, side effects were few and generally mild (gastrointestinal irritation and nausea).

However, many of the studies suffered from design flaws including small (< 10 subjects) sample sizes, heterogeneity of subjects, and short-duration of treatment. Furthermore, there is a lack of multiple studies for many of the individual supplements. Despite the apparent lack of side effects of these treatments, it would be prudent to be aware of the potential for dietary supplements, especially botanicals, to interact with a patientâ€™s prescription medication. One of the most important potential botanical-drug interactions is that of garlic, Trigonella, and Ginkgo biloba with non-steroidal anti-inflammatory drugs (including aspirin) or warfarin, as these botanicals possess limited anti-coagulant activity [553] [554] . Another potential interaction of concern is one involving G. biloba, a botanical widely used for the treatment of memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus, and headache [555] [556] . Ingestion of G. biloba extract by patients with T2D may increase the hepatic metabolic clearance rate of not only insulin but also hypoglycemic medications, resulting in reduced insulin-mediated glucose metabolism and elevated blood glucose [557] . Another issue to consider with botanicals is the potential for batch-to-batch variation due to age of the plant, geographic source, time of harvest, and method of drying and preparation, all of which can dramatically impact the purity and potency of active ingredients. None of the agents discussed here is recommended for use in pregnant or lactating women, or in children. Furthermore, patients should be advised on the proper use of any alternative treatment to avoid the risk of hypoglycemia.

That being stated, several botanical and nutraceutical agents merit consideration as complimentary approaches for use in patients with T2D. Botanical treatments with the strongest evidence of clinical safety and efficacy include I. batas (caiapo), T. foenum-graecum (fenugreek), and C.cassia (cinnamon). Non-botanical nutraceutical agents with promise for improving insulin sensitivity and glycemic control include Î±-lipoic acid, chromium picolinate, and magnesium. If the safety profile of the newly proposed organic vanadium complexes could be

confirmed with chronic use, this agent would also be regarded as a promising treatment for glycemic control. In addition, there is evidence that Î±-lipoic acid improve the symptoms of individuals with microvascular complications, especially neuropathy. Clearly, Ï‰-3 PUFAs (EPA, DHA, Î±-linolenic acid) merit strong consideration for lipid lowering, and overall cardiovascular health.

The increasing movement for the public in general and patients with diabetes (and other diseases) to self-treat using botanicals and nutraceuticals cannot be disputed and should not be ignored. Health care professionals are urged to increase their knowledge base in this area on an ongoing basis. They are also urged to pro-actively query patients on their use of these agents, and record the information obtained in the patient record. Many patients are reluctant to discuss their use of botanicals and nutraceuticals, so it is important for health care professionals to keep an open mind and be non-judgmental. Since patients cannot be expected to distinguish between the marketing hype of manufacturers and evidence derived from credible scientific studies, health care professionals must be positioned to provide an informed opinion and recommendation.

TABLES

Table 1. Major Botanicals Used for Type 2 Diabetes

Botanical	Putative Bioactives	Anti-Diabetic Activity	Mode of Action	Typical Daily Dose	Potential Side Effects	Relative Rating
I. batas (Caiapo)	High-molecular weight acid glycoprotein	Glucose control; reduces HbA_{1c}	Not well characterized; Possibly increases insulin sensitivity	4 g of white-skin sweet potato (capsule)	None reported	++++
T. foenum-graecum (Fenugreek)	Fiber, 4- hydroxyisoleucine, saponins, coumarins, alkaloids, glycosides	Glucose control; Anti- hyperlipidemic	Delays gastric emptying; Inhibits glucose absorption in gut; Enhances insulin secretion	2.5-15 g (defatted seeds)	Hypoglycemia; Additive with other glucose-lowering agents and insulin; GI irritation; Anti-coagulant	+++
C. cassia (Cinnamon)	Methyl hydroxyl chalcone polymer (MHCP)	Glucose control	Possibly insulin mimetic	3-6 g (capsule)	None reported	+++

Botanical	Putative Bioactives	Anti-Diabetic Activity	Mode of Action	Typical Daily Dose	Potential Side Effects	Relative Rating
M. charantia (Bitter melon)	Charantin, vicine, mormordicine (alkaloid), polypeptide P	Glucose control	Inhibits glucose absorption in gut; Enhances insulin secretion; increases glucose transport and glycogen synthesis	300-600 mg (juice extract); 1.8 g (capsule)	Hypoglycemia; Additive with other glucose-lowering agents and insulin; GI irritation	++
G. sylvestre (Gurmar)	Gymnemic acids, gymnemosides	Glucose control	Inhibits glucose absorption in gut; Enhances insulin secretion	200-600 mg	Hypoglycemia; Additive with other glucose-lowering agents and insulin;GI irritation	++
O. streptacantha (Nopal; prickly pear)	Fiber, pectin	Glucose control; Anti- hyperlipidemic	Delays gastric emptying; Inhibits glucose absorption in gut	2.4 g	None reported (limited data)	++
C. indica	Not yet characterized	Glucose control	Not characterized; possibly insulin mimetic	1.8 g (powdered leaves)	None reported (limited data)	++
P. quinquefolius (American ginseng)	Ginsenosides (saponins), polysaccharides, peptides, fatty acids	Glucose control	Delays gastric emptying; Inhibits glucose absorption in gut; Hormonal & CNS activity	100-200 mg	Estrogenic effects; Ginseng abuse syndrome; Interacts with many drugs	++
A. vera	Fiber (gluco	Glucose	Not charact	1.2 g	None	++

Botanical	Putative Bioactives	Anti-Diabetic Activity	Mode of Action	Typical Daily Dose	Potential Side Effects	Relative Rating
(Aloe)	mannan), aloins, anthraquinones, barbaloin, polysaccharides, salicylic acids	control	erized; possibly delays gastric emptying and inhibits glucose absorption in gut	(capsule)	reported (limited data)	
A. sativum (Garlic)	Allicin, allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate, Î³-L-glutamyl- S-alkyl-L-cysteine	Anti- hyperlipidemic;Anti-hypertensive	Anti-inflammatory (Antioxidant)	600-1000 mg	GI irritation; Anti-coagulant; heartburn; garlic odor	+

Table 2. Major Non-Botanical Nutraceuticals Used for Type 2 Diabetes

Botanical	Anti-Diabetic Activity	Mode of Action	Typical Daily Dose	Potential Side Effects	Relative Rating
Ï‰-3 PUFAs	Anti-hyperlipidemic	PPARÎ±,Î³,Î´ agonists	0.65-1.2 g (EPA + DHA); 2.4 g ALA	GI irritation; halitosis	+++++
Î±-Lipoic acid	Insulin sensitizer; Anti-neuropathy	Anti-inflammatory (Antioxidant)	900-1800 mg	GI irritation	++++
Chromium	Glucose control	Enhances insulin action	200-400 Î¼g	Potential for renal toxicity (rare)	++++
Magnesium	Insulin sensitizer; Glucose control; Anti-hypertensive	Not characterized; Possibly enhances insulin action	300-400 mg; (2.5 g used for glucose control)	Diarrhea	++++
Zinc	Glucose control	Anti-inflammatory (Antioxidant); insulin binding	30-80 mg	GI irritation; metallic taste; headache	+++
L-Arginine	Improves endothelial	Nitric oxide donor	3-6 g	None reported	+++

Botanical	Anti-Diabetic Activity	Mode of Action	Typical Daily Dose	Potential Side Effects	Relative Rating
	dysfunction				
Vitamin C	Insulin sensitizer; Improves endothelial dysfunction	Anti-inflammatory (Antioxidant)	500-2000 mg	None reported	++
Coenzyme Q 10	Insulin sensitizer	Anti-inflammatory (Antioxidant)	100-150 mg	GI irritation	+
Vitamin E	Insulin sensitizer	Anti-inflammatory (Antioxidant)	600-900 mg	None reported	Not recommended
Vanadium	Insulin sensitizer; Glucose control	Insulin mimetic; Pan-tyrosine phosphatase inhibitor	100-150 mg	GI irritation; tissue accumulation; Uncertain long-term safety profile	Not recommended for long term human use
CLA	Anti-obesity	PPARÎ± agonist	2-4 g	GI irritation; Increased inflammation and oxidative stress	Not recommended
Niacin	Anti-hyperlipidemic	Anti-lipolytic; decreases rate of hepatic synthesis of VLDL and LDL	1000-1500 mg	Impaired glucose tolerance; flushing	Available as Rx

Table 3. Credible Internet Sources for Information on Botanicals and Other Nutraceuticals

Source	Website Address	Thumbnail Sketch
American Botanical Council	http://www.herbalgram.org/	The leading independent, non-profit, international member-based organization providing education using science-based and traditional information to promote the responsible use of herbal medicine
American Nutraceutical Association	http://www.ana-jana.org/	A professional organization founded to develop and provide educational materials

Source	Website Address	Thumbnail Sketch
		and programs on nutraceuticals and nutrition for health care professionals and consumers
American Society of Pharmacognosy	http://www.phcog.org	Professional organization dedicated to discipline of pharmacognosy (the science and study of drugs from natural sources)
The Cochrane Library	http://www.nelh.nhs.uk/cochrane.asp	An electronic database designed to provide high quality scientific evidence
Consumer Lab.com	http://www.consumerlab.com	Independent product review site that provides information on the content of nutritional products including dietary supplements (Subscription required for access to some content)
DiaMedBase	http://www.progenebio.in/DMP/DMP.htm	An interactive database of approximately 400 medicinal plants for diabetes
Dr. Dukeâ€™s Phytochemical and Ethnobotanical Databases	http://www.ars-grin.gov/duke/	An interactive, electronic database developed by James Duke, PhD, former chief botanist at the USDA
HerbMed	http://www.herbmed.org/index.asp	An interactive, electronic herbal database on the use of herbs for health
MD Anderson Complementary/ Integrative Medicine	http://www.mdanderson.org/departments/CIMER/	Website of prestigious cancer treatment center
National Center for Complimentary and Alternative Medicine	http://nccam.nih.gov ; http://nccam.nih.gov/health/diabetes/	National (US) center that supports and disseminates research results on complementary and alternative medicine; NCCAM research report (2005): Treating type 2 diabetes with dietary supplements
Natural Medicines Comprehensive Database	http://www.naturaldatabase.com	An extremely comprehensive, scientifically-based, and practical database on natural medicines (Subscription required)

Source	Website Address	Thumbnail Sketch
NIH Office of Dietary Supplements (ODS)	http://ods.od.nih.gov/index.aspx	National (US) center that supports and disseminates research results on dietary supplements
NAPRALERTâ„¢: Natural Products Alert	http://www.napralert.org/	NAPRALERTâ„¢ is an extensive relational database developed at the University of IL at Chicago, and contains ethnomedical, chemical, biochemical, pharmacological, and clinical data derived from the evaluation of plants and other natural products (Search charges apply)
National Institute of Diabetes& Digestive & Kidney Diseases: Alternative Therapies for Diabetes	http://diabetes.niddk.nih.gov/ http://diabetes.niddk.nih.gov/dm/pubs/alternativetherapies/index.htm	Clearinghouse (albeit abridged) for some alternative treatments for diabetes
Quackwatch	http://www.quackwatch.org/	A non-profit corporation whose purpose is to combat health-related frauds, myths, fads, fallacies, and misconduct
Rick Mendosa's Diabetes Directory	http://www.mendosa.com/ http://www.mendosa.com/diabetes.htm	An extensive and unbiased private site published by a freelance journalist and consultant specializing in (and afflicted with) diabetes
Supplement Watch	http://www.supplementwatch.com	A self-funded, privately held corporation consisting of scientists, physiologists, nutritionists, and other health professionals dedicated to educating the public about the pros and cons of dietary supplementation. (Subscription required for access to some content)
US FDA Office of Nutritional Products, Labeling, and Dietary Supplements	http://www.cfsan.fda.gov/ http://www.cfsan.fda.gov/~dms/supplmnt.html	FDA office responsible for developing policy and regulations for dietary supplements, medical foods, and related areas, as well as for their scientific evaluation
WebMD Health	http://www.webmd.com/	WebMD provides

Source	Website Address	Thumbnail Sketch
		comprehensive health information and tools for managing health care. For health care professionals and their patients
N.B. Sources cited above are selected examples, and not meant to be exhaustive		

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