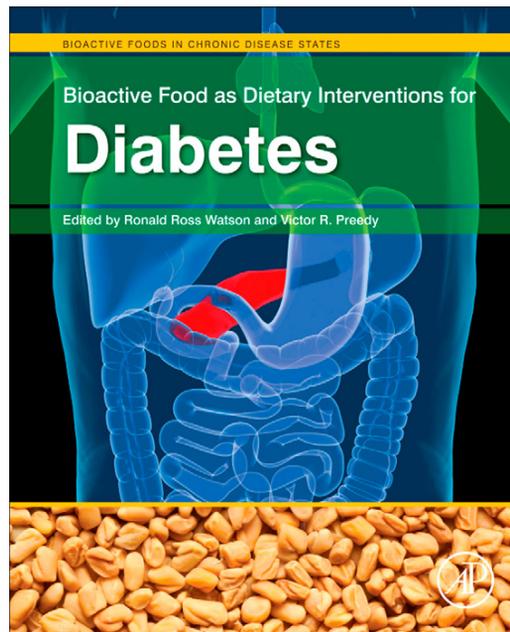


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## CHAPTER 30

# Phytonutrients in Diabetes Management

**R. Jaffe**

Health Studies Collegium, Ashburn, VA, USA

This chapter discusses various nutrients found beneficial in the clinical management of diabetes. Individual needs can now be determined through functional, predictive tests whose ranges are set to reflect maximum risk reduction or health gained. This approach requires a detailed review of patient history and current situation. Personalized predictive care of diabetics is described here. Over 90% of diabetes risk is avoidable or reversible when healthier life style choices are practised.

## 1. CLINICAL PERSPECTIVE

Tracking patient progress, particularly with the use of lab tests, can be helpful in targeting and personalizing nutritional diet and supplement predictive plan. It is important to remember that these kinds of clinical interventions rely heavily on patient information, inspiration, incentives and compliance. Such engaged healthcare teams invite greater participation by consumers. This calls for ongoing support and encouragement by the clinician.

## 2. SPECIFIC NUTRIENTS

Two of the primary issues in nutrient supplementation for diabetics are dietary deficiencies and increased nutrient requirements due to the loss of homeostasis and immune tolerance that occur early in the processes. This starts with insulin resistance, progress through metabolic syndrome to abdominal obesity and onto prediabetes, diabetes and all the vascular consequences including the heart and related organs (Jaffe and Mani, 2009). Individuals in certain populations such as the young, infirm and the elderly are at increased risk of frank deficiencies due to maldigestion, enteropathy, and dysbiosis. A second issue involves higher nutritional requirements due to epigenetic and genetic factors, the demands of metabolic stress, pro-oxidant environmental toxins, or medication (Filion et al., 2009). Many forms of metabolic stress increase the nutrient consumption burn rate, including excessive carbohydrate intake.

## 2.1 Vitamin Sufficiency

Nutrient supplementation is essential for proactive prevention and also for the best outcome therapy. Supplementing essential and conditionally essential nutrients to support essential metabolic pathways is required for immune defense and repair, neuro-hormone balance as well as digestive and detox competencies.

### 2.1.1 Carotenoids

Impaired antioxidant status has been shown to have a definite role in the development of insulin resistance and type 2 diabetes (Arniöv et al., 2009). The CARDIA study showed that higher serum carotenoid concentrations were associated with lower risk of diabetes and insulin resistance in nonsmokers (Hozawa et al., 2006). Serum carotenoids are inversely associated with type 2 diabetes and impaired glucose metabolism. In type 3 diabetes, diabetes-induced learning and memory compromise is characterized by impaired cognitive functions and neurochemical and structural abnormalities, which involve direct neuronal damage caused by excess intracellular glucose. Earlier research has shown that carotenoids such as lycopene improve cognitive health and memory-induced learning in diabetes (Kuhad et al., 2008). Mixed natural carotenoids are consistently helpful. High doses of isolated beta carotene, however, are not recommended.

### 2.1.2 Vitamin B complex including folinate (folates)

Folic acid supplementation, helpful in lowering homocysteine, has also been found to improve endothelial dysfunction in type 2 diabetes (Title et al., 2006). For optimum homocysteine levels, a protocol that includes folate, B<sub>12</sub>, B<sub>6</sub>, and methyl donors such as TMG (betaine), is recommended, especially for those on long-term metformin medication and prone to vitamin B<sub>12</sub> deficiency (de Jager et al., 2010). We prefer forms dissolved under the tongue for more predictable uptake. We suggest sufficient methylation factors to bring the homocysteine to <6 µmol/L. Clinically, this means enough B-complex to keep the urine a healthy sunshine yellow.

### 2.1.3 Biotin

Biotin plays an essential role in glucose metabolism. Biotin improves the diabetes by epigenetically repressing gluconeogenic genes (responsible for the production of glucose) and their transcription factors through an insulin-signaling pathway. A combination of chromium and biotin has been found particularly effective in improving glycemic control in individuals with diabetes (Albarracin et al., 2008). Biotin may also reduce pain from diabetic neuropathy.

### 2.1.4 Ascorbate

Low ascorbate concentrations are seen in diabetics even with usual ascorbate intakes (Sinclair et al., 1994). Recent evidence has suggested that diabetic microangiopathy is

associated with increased free-radical-induced oxidative damage. Ascorbate is a valuable antioxidant and an excellent free radical scavenger. The role of ascorbate is significant. Given the potential for oxidative damage, complications are further compounded when ascorbate levels are low (Jennings et al., 1987). A simple self-assessment can provide the clinician and patient with a clear idea of ascorbate saturation levels and future need. The ascorbate calibration protocol or 'C Cleanse' is an effective method for assessing individual physiological need for ascorbate at any given time. We recommend only ascorbates that are certified as fully reduced, fully buffered, and 100% L-ascorbate. Details of how to determine individual ascorbate needs are available online at <http://www.PERQUE.com>.

## **2.2 Intermediates and Cofactors**

Though this group of nutrients does not fit in the category of essential nutrients, in diabetic patients they are conditionally essential and their intake has produced significant benefits in outcome studies.

### **2.2.1 Choline citrate**

Choline, in conjunction with methionine, has been found to improve myocardial dysfunction associated with the diabetic state in an animal model – in particular abnormal lipid accumulation in the myocardium that can be involved in congestive heart failure, which is frequently diagnosed in individuals with diabetes mellitus. Choline also increases circulating insulin concentrations by increasing muscarinic and nicotinic cholinergic neurotransmission in insulin-secreting beta cells.

Choline in citrate form is alkalinizing, and it enhances magnesium absorption. Neutral micellar droplets form in the gut when magnesium ions, quarternary amines, and citrate or malate are concurrently present. We use choline citrate 1300 m or one teaspoon in water or any beverage taken 1–4 times daily. Concurrent intake of magnesium facilitates uptake of this essential, often deficient mineral.

### **2.2.2 Alpha lipoic acid**

Alpha lipoic acid is a potent natural antioxidant that appears to be insulin-sensitizing. This important cofactor has been found to reduce symptoms of peripheral neuropathy, and at doses of 600 mg daily for 5 weeks, significantly reduced neuropathic pain. We prefer to enhance and regenerate alpha lipoic acid through the sparing and enhancing effects of ascorbate.

### **2.2.3 CoQ<sub>10</sub>**

CoQ<sub>10</sub> is an intermediate compound produced in the healthy body that provides important antioxidant functions. However, its production can easily be impaired by multiple pathological, biochemical, or environmental factors, such as insulin resistance or exposure

to toxic metals. This can result in inadequate levels of CoQ<sub>10</sub>, compromising the body's ability to deal with the inflammatory and oxidative consequences of many common health conditions and pathologies. CoQ<sub>10</sub> is a crucial component of energy-producing function of mitochondria, involved in the production of adenosine triphosphate (ATP). When levels of this nutrient are low, there is also impairment in the function of the electron transport system.

CoQ<sub>10</sub> protects the endothelial lining of the capillaries that are especially vulnerable in diabetics. Insulin resistance is a major cause of stress on the entire vascular system, in particular the capillaries and arteries. CoQ<sub>10</sub> has also been shown to be highly cardioprotective, and conversely CoQ<sub>10</sub> deficiencies are commonly associated with congestive heart failure. As an intermediate, CoQ<sub>10</sub> is also protective against the side effects of certain medications, particularly statins. We use CoQ<sub>10</sub> micellized in 100% rice bran oil including gamma oryzanol and natural tocopherols. Typical repletion doses are 300–1200 mg day<sup>-1</sup> for 1–3 months. Maintenance doses of micellized CoQ<sub>10</sub> with mixed natural tocopherols are 60–300 mg day<sup>-1</sup>.

#### **2.2.4 Polyphenolics: Quercetin dihydrate, OPC, Resveratrol, Curcumin**

Quercetin dihydrate and soluble OPC are our preferred polyphenolics. The combination of these distinctive flavonoids and flavonols is safer and more effective at stimulating repair and reducing inflammation. Freeze-dried pomegranate juice is another helpful addition to a polyphenolic supplement. Resveratrol is a natural polyphenolic produced by plants to provide resistance against bacteria and fungi. Primarily found in the skin of certain fruits including red grapes, and in high levels in red wine, researchers believe it to be one of the factors in the French Paradox. In animal studies, resveratrol was shown to have anti-inflammatory effects, inhibiting both acute and chronic phases of inflammation. Additionally, this cofactor has been found to have properties that lower blood sugar and are cardioprotective, and resulting improvements in glucose regulation have been confirmed in a human clinical trial. High doses of resveratrol of 3–5 g significantly lowered blood sugar when provided in a proprietary formulation designed to enhance bioavailability. Resveratrol also appears to have effects that mimic the biochemical benefits of calorie restriction. Other studies report benefit from curcumin polyphenolics through turmeric.

These plant-based, water-soluble phytonutrients include a number of biochemicals with known medicinal properties, including certain black teas with antioxidant properties, as well as tannins, aromatics (such as gallic, which is present in witch hazel and tea leaves), and flavonoids (such as quercetin), shown to have anti-allergic and anti-inflammatory effects.

Quercetin is a flavonoid found primarily in fruits and vegetables, which has powerful vasodilating and antioxidant effects in endothelial dysfunction conditions such as diabetes. More recently, quercetin has also been shown to potentiate insulin secretion, protect b-cell function, and prevent oxidative damage. The combination of quercetin dihydrate

with soluble orthoproanthocyanidins (OPC), particularly at a ratio of 100:1, can provide improved bioactivity.

### 2.3 Essential Fatty Acids

Intake of total, saturated and/or monounsaturated fat has been associated with increased risk of type 2 diabetes. Conversely, the merit of increasing healthy essential fatty acids is widely acknowledged and a lower incidence of type 2 diabetes is seen in individuals who consume omega-3 fatty acids. We use only the marine lipids that are distilled under nitrogen to protect eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from oxidative damage and to remove toxic minerals.

#### 2.3.1 Omega-3 fats

Omega-3 fatty acids have been found to improve vascular function and reduce inflammation in diabetes. The omega-3 fatty acid pathway can be supplemented at multiple levels. One approach is to use alpha-linolenic acids from flax oil. However, flax oil is not a reliable source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), because alpha-linolenic acid (ALA) is frequently burned as an energy source. Other glitches in conversion can occur in the numerous metabolic steps in the omega-3 pathway that requires conversion of ALA into EPA (and later in the pathway, to DHA). For supplementation, fish oil provides nutritionally significant quantities of EPA. Clinically, we suggest 2–9 g day<sup>-1</sup> of EPA/DHA. ALA is also an omega-3 fatty acid, however, its poor conversion to active EPA and DHA makes it unsuitable as a supplement. Krill and algae are the other sources of DHA. While some suggest EPA for body and DHA for brain, we find both helpful and needed by both.

#### 2.3.2 Rice bran oil and gamma oryzanol

In diabetes, the most common lipid abnormalities are hypertriglyceridemia and hypercholesterolemia. Rice bran has been found to support better lipid metabolism. In addition, rice bran has been shown to improve both insulin resistance and hyperglycemia in diabetes. One of the primary constituents of rice bran oil is gamma oryzanol, a group of ferulate esters of triterpene alcohols and phytosterols. These esters have been recognized for their effects in supporting antioxidant activity, improvement of pituitary secretion, and inhibition of platelet aggregation. We use this to disburse and enhance uptake of CoQ<sub>10</sub>. This is also healthy cooking oil.

### 2.4 Amino Acids Taurine and Glutamine

Certain amino acids offer a significant value due to their antioxidant properties. Taurine is considered a conditionally essential amino acid along with glutamine, lysine, and tryptophan. Lower tissue concentrations of taurine have been associated with many pathological states, including diabetes. This amino acid has been shown to regulate

intracellular  $\text{Ca}^{2+}$  concentration, act as a neuromediator and neuromodulator, support osmoregulation and cholic acid production, and modulate inflammatory reactions. Deficiencies of taurine and other amino acids can result from a low protein diet; additionally, increased intracellular concentrations of sorbitol can deplete taurine levels. Taurine supplementation has beneficial effects on platelet aggregation, and in neuropathy, cardiomyopathy, nephropathy, and retinopathy. Biochemically, taurine's impact as a sulfonyl derivative is a key aspect of its therapeutic function, because sulfur-based amino acids are involved in so many crucial interactions throughout the body. Clinically, taurine provided in tandem with vanadium has shown synergistic effects. Adequate ascorbate intake conserves and helps recycle taurine. Restoring healthy digestion is important to proper amino acid availability. Glutamine is important for energy not only in the digestive tract, but also in the brain and muscle. Since the needs are high, there is a tendency to take in high doses of glutamine, which can lead to the accumulation of the excitatory neurotoxin glutamate. To avoid this, we use the formulation of L-glutamine with pyridoxal alpha ketoglutarate (PAK). This combination recycles glutamine making more available for the body to use and prevents the effects of glutamate.

## 2.5 Minerals

Deficiencies of both trace minerals and macrominerals play a major role in the development of impaired insulin–glucose metabolism. Assessment for mineral status and replacement of deficiencies can be critically important, particularly for certain mineral essential for diabetes management. Foremost among these are chromium, vanadium, and magnesium, though deficiencies of other trace minerals can also complicate recovery. Additional trace minerals that have roles in glucose and insulin metabolism include zinc, copper, iron, molybdenum, manganese, and selenium as selenomethionine.

### 2.5.1 Calcium and magnesium

While calcium and magnesium are frequently discussed in a relationship, magnesium is generally more important in the clinical management of diabetes due to the higher likelihood of its deficiencies. Magnesium is the second most abundant intracellular cation in the body. This mineral is a critical cofactor in more than 300 enzymatic reactions (Coudray et al., 2005), many of them involved in glucose metabolism. Magnesium status is frequently altered in individuals with type 2 diabetes. Magnesium has been shown to play an important role in blood glucose control (Sales et al., 2011). In the general population, the incidence of insulin resistance and metabolic syndrome tends to correlate with the availability of magnesium in the diet. Oral magnesium supplementation has been found to improve insulin sensitivity even in overweight, nondiabetic subjects with normal magnesium levels, emphasizing the need for an early optimization of magnesium status to prevent insulin resistance and subsequently type 2 diabetes (Mooren et al., 2011).

Magnesium absorption can be enhanced by supplementing this mineral in combination with choline citrate. This facilitates magnesium uptake through neutral pores bypassing the usual calcium–magnesium ATPase enzyme system that can be disrupted by toxic minerals or xenotoxins. In terms of bioavailability, magnesium ionized with citrate, malate, succinate, fumarate, glycinate, or ascorbate is more absorbable (Walker et al., 2003). Poor availability of magnesium oxide, carbonate, sulfate, or magnesium chelated with soy peptides is but one of the reasons that they are not the best choices. We find that magnesium uptake block is overcome when choline citrate is concurrently taken. We suggest supplementation with 440–800 mg day<sup>-1</sup> elemental magnesium taken with choline citrate to enhance uptake.

### **2.5.2 Chromium and vanadium**

Chromium has been established as an essential trace element in humans for normal carbohydrate metabolism (Balk et al., 2007). This key trace mineral is thought to facilitate insulin signaling and therefore may improve insulin sensitivity (Cefalu et al., 2010). Modulation of lipid metabolism by chromium in peripheral tissues may represent an additional novel mechanism of action (Cefalu and Hu, 2004). Chromium supplementation in doses of 1000 µg day<sup>-1</sup> has shown desired clinical response in insulin-resistant individuals with type 2 diabetes, especially in those who have elevated fasting glucose and hemoglobin HbA1c levels (Wang and Cefalu, 2010).

Vanadium has been found to mimic the effects of insulin, stimulating glucose uptake without affecting endogenous levels (Garcia-Vicente et al., 2007). As a supplement, chromium citrate and picolinate as well as vanadium ascorbate can increase lean body mass, reduce weight, and decrease visceral fat when used in combination with oral hypoglycemic medications. Reduced levels of this water-soluble mineral can occur due to strenuous exercise, infection, high stress, pregnancy, or physical trauma, as well as steroid medications and iron supplements, and this effect has since been replicated in numerous studies in an animal model (Kent, 1999). Vanadium has been shown to improve sensitivity to insulin in both type 1 and type 2 diabetes, and also to lower cholesterol levels and blood pressure (Bhanot and McNeill, 1994). We suggest intake of 200–600 µg day<sup>-1</sup> of chromium citrate or picolinate plus 100–300 µg day<sup>-1</sup> of vanadium ascorbate.

### **2.5.3 Iodine and iodide**

Thyroid disorders are more prevalent in individuals with diabetes, mirroring other trace mineral deficiencies documented in diabetics (Sales and Pedrosa, 2006). Regular screening for thyroid abnormalities in all diabetic patients allows for early and prudent treatment of subclinical thyroid conditions (Johnson, 2006). The interaction between insulin and thyroid function is intricate. For example, compromises in insulin receptor function can lead to phosphorylation of cytoplasmic proteins (termed insulin receptors

substrate proteins or IRS) (Cefalu, 2000). It is to be noted that although iodine is essential for normal thyroid functions, certain man-made forms of iodine are more toxic. We recommend 3–5 servings per week of sea vegetables for those seeking lower risk of diabetes.

#### **2.5.4 Sodium and potassium**

The greatest risk perceived with increased sodium is hypertension. An average American consumes ~6–18 g (one to three tablespoons) of ordinary table salt (sodium chloride) each day. The American Diabetes Association recommends a daily sodium intake of 2400 mg (approximately one teaspoon a day or less) for diabetics and those with mild to moderate high blood pressure. Low sodium is also recommended to stall future complications such as diabetic retinopathy (Roy and Janal, 2010).

Acidosis present during diabetes and high blood glucose levels work together to cause fluid and potassium to move out of the cells into blood circulation. Yet, patients with diabetes often also have diminished kidney capacity to excrete potassium into urine. These issues can cause hyperkalemia (Foo et al., 2003). Potassium supplement and close monitoring of potassium levels may reduce the occurrence of dangerous hyperkalemia (Juurlink et al., 2004) so that the potential benefits of high normal potassium could be realized without risk (Khaw and Barrett-Conner, 1987). Acidosis and hypertension are increased by sodium chloride. The same amount of sodium as citrate lowers blood pressure as it alkalinizes. Our emphasis on sodium obscures the role of chloride and acidosis in the more fundamental cause.

On the other hand, magnesium (Mg) and potassium (K) deficiencies occur frequently in diabetics. Because of the vasoconstrictive effects of hypomagnesemia and hypokalemia and the adverse effects of Mg and K deficiencies on carbohydrate metabolism, routine magnesium supplementation of all diabetics may be helpful in reducing diabetic vascular disease (Whang and Sims, 2000). Metabolic acidosis induced mineral wasting is the rule in most diabetics. Integrative management employs the alkaline way to reverse these risk factors. (More details in Chapter 1: The Alkaline Way in Digestive Health). First morning urine pH measurement is recommended with a goal of 6.5–7.5 for the first void after six or more hours of rest.

#### **2.5.5 Zinc, copper, and iron**

Zinc (Zn), copper (Cu), and iron (Fe) are essential minerals that are required to maintain the normal structure, function, and proliferation of cells. Abnormal metabolism of these minerals promotes diabetes and diabetic complications (Zheng et al., 2008).

Low serum zinc level in type 2 diabetes has been shown to be a risk factor for coronary heart disease. The role of zinc in inhibiting atherogenesis has been attributed to antioxidant-like properties, and its function in the manufacture of insulin and facilitation of numerous enzymatic reactions (Soinio et al., 2007). Iron must be ferrous (reduced iron)

to be useful to the body. Low ascorbate means a high oxidation state and more ferric (oxidized iron). Adequate ascorbate intake reduces ferric to ferrous iron, thus preventing this oxidative risk. While ascorbate increases iron uptake from the gut in people deficient in iron, our experience is that ascorbate does not increase iron uptake in people with sufficient iron.

### 3. BOTANICALS

Targeted use of standardized, active botanicals can reduce diabetes risks. Botanical use is typically focused on primary treatment goals. Maintaining healthy blood glucose levels and enhancing immune defense repair systems are the key to better outcomes. There are a number of botanicals that serve as novel glucose-regulating agents. Other goals include reduction of the damaging effects of free radicals and cumulative repair deficits. This means better functional management of the many expressions of inflammation. Botanicals with reported efficacy in the management of diabetes are outlined below.

#### 3.1 Phytonutrients

Phytochemicals with physiological properties include a number of herb- and plant-based constituents with active properties that improve glucose metabolism and lipid levels and provide beneficial antiatherogenic and hormonal effects. We use only the assayed or standardized ingredients. This avoids the all too common disconnection between labeled ingredients that lack activity and may be contaminated. While accurate labeling is important, additional benefit is derived from using ingredients that are helpful once inside the body.

##### 3.1.1 *Banaba (Lagerstroemia speciosa L.)*

Corosolic acid, an active component of Banaba leaves (*Lagerstroemia speciosa L.*), has hypoglycemic and hypocholesterolemic effects. Corosolic acid inhibits gluconeogenesis and stimulates glucose uptake. An oral dose of 1% corosolic acid at 48 mg day<sup>-1</sup> in a soft gel format has been found to support 30% improvement in glucose levels.

##### 3.1.2 *Bitter melon (Momordica elegans)*

Extract of bitter melon in supplement form has been widely used as a traditional medicine for diabetic patients in Asia. Alone it has a modest hypoglycemic effect at doses of at least 2000 mg day<sup>-1</sup>. This botanical supplement enhances the cellular uptake of glucose and promotes insulin release, potentiating its effect, and in animal studies, has been shown to increase the number of insulin-producing beta cells in diabetic animals. Bitter melon also reduces adiposity and oxidative stress in addition to reducing blood triglycerides and low-density lipoproteins. Dietary use of bitter melon or its juice decreases blood glucose levels, increases HDL-cholesterol, and decreases triglyceride levels, thus exhibiting anti-atherogenic qualities.

### **3.1.3 Fenugreek (*Trigonella foenum-graecum*)**

Perhaps the most studied herb in the management of diabetes, fenugreek has been found to lower both blood glucose and lipids. Fenugreek decreases insulin resistance and decreases triglyceride levels. Fenugreek can safely be used as an adjunct and in combination with sulfonylureas in the treatment of type 2 diabetes. Extracts from this herb have been shown to decrease lipid content of liver, inhibit gluconeogenesis, stimulate glycolysis, and overall to be more effective, with fewer side effects than the commonly prescribed medication tolbutamide.

### **3.1.4 French lilac (*Galega officinalis*)**

*Galega officinalis* plant has been known since the Middle Ages as a folk remedy for relieving the symptoms of diabetes mellitus. The active ingredient in this plant that decreases blood sugar by decreasing insulin resistance is galegine or isoamylene guanidine.

### **3.1.5 Huckleberry/bilberry (*Vaccinium myrtillus*)**

Bilberry has been used traditionally in the treatment of diabetes, and research suggests that its leaf extract can lower blood sugar levels.

### **3.1.6 Chaste tree berry (*Agnus castus*)**

*Agnus castus* improves function of the hypothalamic–pituitary–adrenal axis, enhancing the often overlooked but important hormonal influence of this system on blood glucose regulation. Hormonal dysregulation and distress increase risk from syndrome X and insulin resistance, as well as associated complications.

### **3.1.7 Magnolol (*Magnolia officinalis*)**

This bioactive compound found in the bark of the Houpu magnolia, used in Chinese herbal medicine, has been shown to be helpful in the management of diabetes and metabolic syndrome. The use of magnolol (*Magnolia officinalis*) can improve blood glucose control and prevent or slow the development of complications such as diabetic nephropathy. In conjunction with *Phellodendron amurense*, magnolia can regulate adrenal stress hormones such as dehydroepiandrosterone and cortisol, which can be imbalanced in the diabetic state and in metabolic syndrome.

### **3.1.8 Golden root (*Rhodiola rosea*)**

*Rhodiola rosea* can be a useful adjunct in diabetic therapy, given pharmacological evidence of use in fatigue and emerging evidence of its effectiveness in supporting cognition and mood. This botanical is used for its adaptogenic properties, which include cardioprotective effects, and improved levels of beta-endorphins. We routinely use a combination of corosolic acid, bitter melon, French lilac, bilberry, *Agnus castus*, chromium, and

vanadium more safely, and effectively bring blood sugar into a healthier range and reduce insulin resistance.

#### 4. NUTRIENT–DRUG PROTOCOLS

Over the last decade, guidelines for the treatment of type 2 diabetes have increasingly favored tighter glycemic control, necessitating the use of more aggressive pharmacological therapies (Filion et al., 2009). Table 30.1 provides an overview of the medications

**Table 30.1** Diabetes Management: Potential Nutrient–Drug Interactions

Pharmacological agents	Mechanism of action	Clinical considerations	Nutrient considerations	Food–diet interactions
<i>Sulfonylureas</i> : first generation medications (chlorpropamide, tolbutamide) and second generation medications (glyburide, glipizide, and glimepiride)	Stimulate insulin secretion by binding to receptors on the pancreatic beta cell; metabolized in the liver via the cytochrome P450 system	Secondary benefit: decrease LDL, increase HDL to normal levels Risks: weight gain; hypoglycemic episodes	Minor	Avoided consumption with alcohol. For glipizide: take 30 min before a meal recommended for optimum results
<i>Meglitinides</i> : repaglinide and nateglinide (glinides)	Similar to sulfonylureas – metabolized in the liver via the cytochrome P450 system	More favorable safety profile than sulfonylureas, especially in patients with renal failure Specific caution with the following medications: rifampicin, ciclosporin, gemfibrozil and repaglinide and also, with statins such as simvastatin and lovastatin	Minor	They have a rapid elimination rate, so recommended to be taken at the beginning of a meal Note: these medications are not to be taken with grapefruit juice as it can enhance the effects of the drug, precipitating hypoglycemia

*Continued*

**Table 30.1** Diabetes Management: Potential Nutrient–Drug Interactions—cont'd

<b>Pharmacological agents</b>	<b>Mechanism of action</b>	<b>Clinical considerations</b>	<b>Nutrient considerations</b>	<b>Food–diet interactions</b>
<i>Biguanides</i> (metformin)	Reduce hepatic glucose production	Metformin: reduction in TG, LDL, total cholesterol, HbA1c and insulin, reducing oxidative stress Can cause GI discomfort, rare lactic acidosis	Folate and vitamin B <sub>12</sub> . Intrinsic factor is calcium-dependent, so supplementation of calcium may be indicated too Increase in homocysteine levels	To minimize GI disturbances, recommended to be taken with food
<i>Thiazolidinediones</i> (rosiglitazone, pioglitazone)	Improve insulin action	Decrease in homocysteine Rosglitazone: Reduction in TG, LDL, total cholesterol, HbA1c and insulin, reducing oxidative stress (1) Increased risk of myocardial infarction and heart failure. (2) Fracture risk in women, and, for rosiglitazone, more rapid bone loss. (3) To be used with caution in people with hepatic dysfunction	Due to risk of bone loss, bone nutrient supplementation is recommended (in post-menopausal women especially)	No effect of food on activity
	Metabolized in the liver via the cytochrome P450 system	Specific caution when combined with statins		

**Table 30.1** Diabetes Management: Potential Nutrient–Drug Interactions—cont'd

<b>Pharmacological agents</b>	<b>Mechanism of action</b>	<b>Clinical considerations</b>	<b>Nutrient considerations</b>	<b>Food–diet interactions</b>
<i>Incretin analogs:</i> Exenatide and rimonabant (injectable)	Stimulate insulin secretion from pancreatic beta cell; slower absorption of carbohydrate from the gut	Accelerated weight loss Possible nausea, diarrhea, vomiting	No specific interactions yet identified	Not to be taken after meals

commonly involved in the pharmacological management of diabetes and summarizes potential nutrient–drug interactions. It is increasingly clear that life–style and natural products are safer and more effective than strict pharmacological control to achieve the same blood sugar levels. The integrative approach to diabetes and sugar metabolism we helped pioneer is increasingly recognized as the preferred treatment guide.

These expanded protocols require additional attention to detail. Antidiabetic medications can increase the need for certain nutrients; for example, metformin increases the requirement for vitamin B<sub>12</sub>. However, the benefits of an expanded pharmacopeia of nutrient and botanical therapies are significant.

Given the growing emphasis on prevention, the use of nutrients and botanicals merit priority in the management of insulin resistance and metabolic syndrome, and in diabetes treatment (Jaffe and Mani, 2009). These products allow greater specificity in meeting the particular needs of the individual patient.

## 5. CONCLUSION

The applications of nutritional support in the treatment of errors in glucose–insulin metabolism are being acknowledged widely. A great deal of active research is currently ongoing that is likely to further elaborate on effective patient management. The clinician is strongly encouraged to continue to monitor emerging research advances. The lower risk, higher gain integrative approach described here and in Chapter 4 (Diabetes as an Immune Dysfunction Syndrome) are recommended. Healthier digestion and detoxification, neuro–hormonal balance and immune defense and repair tolerance yield best outcomes over the continuum of insulin resistance, obesity, metabolic syndrome and diabetes.

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