Herbs for Diabetes

Update—Part 1

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Abstract

The incidence of diabetes mellitus continues to increase, and there is a real need for botanical alternatives, especially for patients with type 2 diabetes (DM2), in whom commonly prescribed medications tend to worsen the condition over time and frequently have unwanted side-effects. Part 1 of this two-part article discusses natural agents that act as potential insulin sensitizers.

The agents covered here include natural insulin sensitizers, such as *Cinnamomum verum* (true or Saigon cinnamon), formerly known as *C. zeylanicum, C. cassia* (cassia cinnamon), formerly known as *C. aromaticum;* berberine-containing plants, such as *Mahonia aquifolium* (Oregon grape), *Berberis* spp. (barberry), *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (coptis, huáng lián); and *Silybum marianum* (milk thistle). Coverage also includes the hypoglycemic immunomodulators *Panax quinquefolius* (American ginseng) and *P. ginseng* (Asian ginseng). Finally, β-cell protectors and regenerators, such as (*Gymnema sylvestre* (gurmar, gymnema) and C spp., are discussed as well as some reports that some botanicals used for patients with DM may have unwanted insulin secretagogue effects.

Introduction

Although the current authors have written two articles on some specific herbs for addressing diabetes mellitus in the past 15 years, an attempt was never made to write a comprehensive discussion about this important subject.[1,2] Much has transpired since those articles were written, and there are many old and new herbal tools to help manage this extremely common problem.

The causes of type 2 diabetes mellitus (DM2) are clear: sedentary lifestyle; eating a high-starch and -sugar diet; not sleeping enough and regularly; chronic high stress; and exposure to numerous chemical toxins, particularly dioxins.[3,4] Fat-soluble diabetes-inducing toxins may be part of the link between obesity and diabetes (as more body fat holds more fat-soluble toxins) and higher rates of diabetes among Native Americans, who consume diets high in fish or sea mammals that bioconcentrate such chemicals.[5,6]

The causes of type 1 diabetes mellitus (DM1) and latent autoimmune diabetes mellitus in adults (LADA) are complex and involve autoimmunity and the interplay of multiple environmental and genetic factors. Therefore, while herbs can play roles in helping people with diabetes mellitus, ultimately, these agents cannot substitute for lifestyle changes to prevent DM2 and to treat both DM1 and DM2, and (with one intriguing exception, plant insulin from *Momordica charantia*) cannot substitute for insulin therapy for DM1. Carefully considered detoxification therapies, as well as avoiding chemical exposures, may also play important preventative and therapeutic roles.[7]

Insulin Sensitizers

Numerous herbs have been shown to act either on insulin receptors or glucose transporters (GLUTs) to enhance the action of endogenous and exogenous insulin (Table 1). Insulin resistance is a key underlying physiologic event in DM2. Herbs that help reduce resistance can be a useful part of treatment of people with—or at risk of developing—DM2, but, ultimately, changes in diet and lifestyle will actually reverse or eliminate insulin resistance. Although insulin-sensitizing drugs, such as metformin, exist and are widely used, they have significant adverse effects, including digestive upset, making natural insulin-sensitizing herbs of great interest. Insulin sensitizers could also enable the use of lower doses of insulin in people with DM1, although this requires careful monitoring, could lead to dangerous hypoglycemia if done improperly, and has not been well-studied.

Cinnamon

The barks from *Cinnamomum verum* (true or Saigon cinnamon), formerly known as *C. zeylanicum,* and *C. cassia* (cassia cinnamon), formerly known as *C. aromaticum*, have received great acclaim as natural insulin sensitizers. A recent meta-analysis reviewed 10 randomized controlled trials of various

Table 1. Summary of Insulin-Sensitizing Botanicals

Herb	Part used	Usual dose	Toxicity concerns
Cinnamomum cassia (cassia cinnamon)	Bark	1–2 g of powdered bark before/during each meal	High coumarin content; potentially hepatotoxic; do not exceed 6 g per day; avoid in patients with severe liver disease
Cinnamomum verum (true cinnamon)	Bark	1–2 g of powdered bark before/during each meal	None
Berberine	Pure compound	500–1000 mg before each meal	None
Panax quinquefolius (American ginseng)	Root	1 g of powdered root with each meal (should contain ~ 2%–3% total ginsenosides, with PPD:PPT 2–3 & Rb1:Rg1 14–17 ratios)	None

PPD, (*20S*)–protopanaxadiol-type saponins; PPT, (*20S*)–protopanaxatriol-type saponins.

cinnamon products and found that they did significantly lower fasting blood glucose (FBG), total cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides while raising high-density lipoprotein (HDL) cholesterol, compared to placebo.[8] There was a large degree of heterogeneity among the trials, including a very wide dose range (120–6000 mg per day), products studied (cassia cinnamon alone in most trials, one trial combining cassia with zinc gluconate and tricalcium phosphate, and two trials not citing what species was used), variable timing around food (before, during, and after used in various trials), and differing statistical analyses.

Hemoglobin A1c (HgbA1c) levels were not affected by cinnamon in this meta-analysis.[8] Overall, this suggests that a wide range of mostly cassia cinnamon products have short-term benefits on blood glucose and lipid management, but these benefits are not maintained for a sufficiently long period of time to reduce HgbA1c.

Another meta-analysis found a significant effect of cinnamon on HgbA1c.[9] Cinnamon has also shown short-term benefits in lowering blood pressure (BP) in patients with diabetes in a meta-analysis of clinical trials.[10] See Mechanisms of Action of Cinnamon Relevant to Insulin for a brief discussion about the mechanisms of action of cinnamon.

Cinnamon is generally quite safe, although there is a concern about cassia cinnamon that warrants use of true cinnamon instead. Cassia cinnamon has considerably high levels of coumarin, a natural molecule that is commonly confused with dicoumarol-derived anticoagulant drugs, such as warfarin, but which, itself, does not produce anticoagulant activity.[11,12] Instead, coumarin in excess is associated with a risk of hepatotoxicity, based on human exposure to the purified compound in levels that can be achieved with high intake of cassia.[13,14] Given that none of the clinical trials on cassia cinnamon have resulted in any cases of hepatotoxicity, levels at or below 6 g per day of cassia powder are likely to be safe for most people.

True cinnamon contains vastly lower levels of coumarin, so it might be wise to use this form, if at all possible, to minimize risk. However, at least one rat study has shown that cassia cinnamon was superior to true cinnamon for lowering FBG. Although true cinnamon was still superior to water in this study, no clinical trials have shown expressly that this species is active, and one clinical trial found that this species had no effect on oral glucose tolerance testing in patients with prediabetes.[15–17] For most patients, reasonable doses of cassia cinnamon are safe and effective.

Berberine

Berberine (Fig. 1) is an isoquinoline alkaloid found in a range of plants including *Mahonia aquifolium* (Oregon grape), *Berberis* spp. (barberry), *Hydrastis canadensis* (goldenseal), and *Coptis chinensis* (coptis, huáng lián). While these herbs and isolated berberine have been used historically for treating gastroenteritis, diarrhea, and other gastrointestinal infections and inflammations; and, topically, for treating inflammatory skin lesions, such as psoriasis, berberine is now also becoming widely researched as a treatment for congestive heart failure and diabetes mellitus.[18]

This effect was first noted in a trial in patients with DM2 and diarrhea.[19] Fourteen clinical trials (most published only in Chinese) of berberine in diabetes mellitus were assessed in a meta-analysis.[20] Compared to placebo, berberine reduced FBG and lipids significantly. Compared to metformin, glipizide, and rosiglitazone, berberine was equally effective for lowering blood sugar while also lowering lipids modestly. The quality of the trials was low. Another meta-analysis (also of generally low-quality studies) concluded that berberine lowers total and LDL cholesterol significantly and triglycerides while raising HDL cholesterol, compared to controls.[21]

A combination of an extract of *B. aristata* (Indian barberry or tree turmeric) containing 85% berberine and an extract of *Silybum marianum* (milk thistle) containing 60% flavonolignans had additive hypoglycemic, hypolipidemic, and hepatoprotective effects.[22] Tetrandrine, an alkaloid from *Stephania tetrandra* (*hàn fáng jǐ*) root, potentiates the hypoglycemic effects of berberine by inhibiting its breakdown in the intestines and liver, thus, increasing its bioavailability.[23]

Berberine is safe for use with metformin, glipizide, glimeprimide, rosiglitazone, and ezetimbe.[20,24] Berberine has been

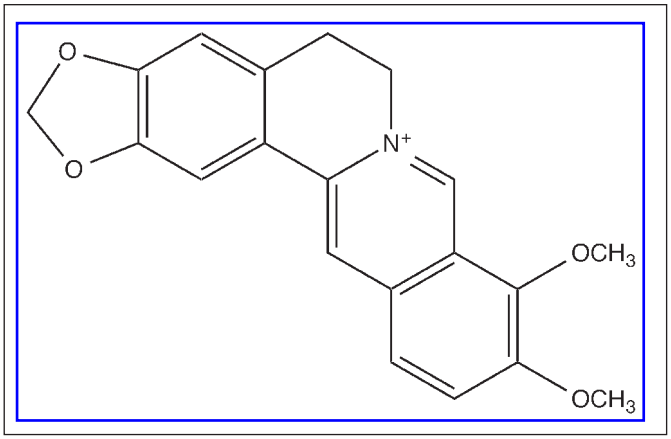

Fig 1. Chemical structure of berberine.

proven to be very safe in general,[25] although there is one reported case of berberine causing bradycardia, atrioventricular block, and junctional rhythm.[26]

Berberine's many mechanisms of action include inhibition of PTP-1B, inhibition of dipeptidyl peptidase IV, and insulinotropic induction of translocation of GLUT-4.[27–29] Double-blinded human trials confirm that berberine is insulin-sensitizing.[30] It also has shown nephroprotective effects in rodent models of diabetic nephropathy.[31]

Hypoglycemic Immunomodulators

Panax quinquefolius (American ginseng) and *P. ginseng* (Asian ginseng) have been studied extensively as hypoglycemic agents. Both plants grow in deciduous forests (American ginseng in the eastern part of North America, and Asian ginseng in Korea and northern China) that have been heavily logged and depleted. The root and rootlets of each herb are most famous as medicines, but other parts may also be usable.

An early controlled trial found that 3 g of crude American ginseng was superior to placebo for improving glycemic control in people with DM2, regardless of whether the ginseng was taken before or after glucose was given in an oral glucose-tolerance test.[32] Another small study in 10 patients with DM2 confirmed that 3 g of crude American ginseng powder was as effective as 6 g or 9 g for lowering postprandial blood glucose.[33]

Two weeks of treatment with low-dose American ginseng root powder (just 1 g daily) was not sufficient to offset the insulin desensitization in healthy volunteers caused by the anti-HIV protease inhibitor drug indinavir.[34] In one failed clinical trial using American ginseng, it was shown that the ginseng product used had significantly lower levels of ginsenosides as well as different ratios of particular ginsenosides, compared to the products used in prior positive trials.[35]

A trial in patients with DM2 found that 3 g of American ginseng root daily was more effective for significantly reducing arterial stiffness and systolic BP, compared to placebo.[36] Asian ginseng showed some benefit (as part of an herbal formula) for helping reduce diabetic nephropathy in one controlled trial.[37] American and Asian ginseng may thus have benefits going beyond blood-glucose control or insulin sensitization.

Red Asian ginseng is made by steaming, then drying, 4–5 year-old main roots of Asian ginseng. A meta-analysis of four clinical trials found no evidence that red Asian ginseng was superior to placebo for improving glycemic control or reducing insulin resistance.[38] Another double-blinded, placebo-controlled, 12-week randomized trial published more recently had similar results.[39] However, a double-blinded, 4-week, randomized trial found that an extract of red ginseng fermented with *Lactobacillus plantarum* at a dose of 2.7 g per day was significantly more effective than placebo for reducing FBG.[40]

White Asian ginseng, which is made from dried, nonsteamed 4–6-year-old main roots, has also been shown, in a dose-escalation trial, to have superior hypoglycemic effects in a single 3-g dose, compared to placebo.[41] There is evidence that lateral rootlets of Asian ginseng have higher ginsenoside content than main roots and that extracts of these rootlets might therefore be more effective.[42] Overall, it is possible that the correct extract and dose of Asian ginseng have still not been determined to realize optimal clinical benefit for patients with diabetes. Currently, however, only fermented red Asian ginseng has shown benefit among various available forms of Asian ginseng, and this benefit was found in only one preliminary clinical trial using white Asian ginseng.

The mechanism of action of ginseng is unclear. In one human trial in adults with atherosclerosis, American ginseng was hypoglycemic, but not insulin-sensitizing.[43] Some research in humans has found a diminution in serum insulin levels in patients with DM2 taking red Asian ginseng, a sign of insulin sensitization.[44] As part of the Chinese herbal formula Tang Yi Kang, 10 g of red Asian ginseng per day was associated with a move toward normalization of the T-helper lymphocyte 1 and 2 ratio, decreased inflammation, and decreased insulin doses in a cohort of patients with LADA.[45] Rodent studies showed a wide range of actions, including insulinotropic, insulin-sensitizing, and hypoglycemic activity, by multiple constituents and molecular mechanisms.[46]

Ginsengs are very safe.[47] Despite much misunderstanding surrounding their use, they do not cause hypertension (but, as shown above, actually decrease BP), and they do not interact negatively with warfarin.[48]

Both American and Asian ginsengs are threatened species in the wild. Only cultivated or wild-simulated product should be purchased to help preserve these precious resources. More research is needed to confirm this. It appears that the fruits are as active as the roots are as hypoglycemic agents, and are possibly stronger.[49] In addition, the fruits are more readily harvested in a sustainable manner, given that picking them does not damage the plant (unlike harvesting the roots, which often kills the plant and certainly sets back its growth immensely). It currently appears that American ginseng is the superior medicine in patients with diabetes mellitus, and that 1 g per day is sufficient, safe, and effective for most. Good quality Asian ginseng root should contain ~ 2%–3% total ginsenosides, with a (*20S*)–protopanaxadiol-type saponins-to-(*20S*)–protopanax-

Mechanisms of Action of Cinnamon Relevant to Insulin

The actions of cinnamon on insulin and glucose are complex and involve multiple constituents, as is so often the case with herbal medicines. Just a small sampling of the many mechanisms and constituents involved are described here.

Protein tyrosine phosphatase-1B (PTP-1B) modulates phosphorylation of insulin and leptin receptors, with differing effects in the periphery and in the central nervous system.[a] Numerous natural products augment the beneficial actions of PTP-1B on leptin and insulin signaling, including cinnamon.[b]

Hydroxycinnamic acids in cinnamon stimulate translocation of GLUT-4 (also known as solute carrier 2A4, or SLC2A4) to the cell membrane which can then uptake glucose.[c–e] This is the action that insulin normally triggers in peripheral cells; this process is downregulated in insulin-resistant states. This action is more correctly described as insulinotropic or insulinomimetic, as it occurs independent of the presence of insulin, but it is indirectly insulin sensitizing. Proanthocyanidins in cinnamon inhibit misfolding on human islet-cell amyloid polypeptide, also considered a crucial factor in development of DM2.[f]

[a]Tsou RC, Bence KK. Central regulation of metabolism by protein tyrosine phosphatases. Front Neurosci 2013;6:192.

[b]Imparl-Radosevich J, Deas S, Polansky MM, et al. Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: Implications for cinnamon regulation of insulin signalling. Horm Res 1998;50:177–182.

[c]Kim W, Khil LY, Clark R, et al. Naphthalenemethyl ester derivative of dihydroxyhydrocinnamic acid, a component of cinnamon, increases glucose disposal by enhancing translocation of glucose transporter 4. Diabetologia 2006;49:2437–2448.

[d]Anand P, Murali KY, Tandon V, et al. Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. Chem Biol Interact 2010;186:72–81.

[e]Shen Y, Fukushima M, Ito Y, et al. Verification of the antidiabetic effects of cinnamon (*Cinnamomum zeylanicum*) using insulin-uncontrolled type 1 diabetic rats and cultured adipocytes. Biosci Biotechnol Biochem 2010;74:2418–2425.

[f]Jiao L, Zhang X, Huang L, et al. Proanthocyanidins are the major anti-diabetic components of cinnamon water extract. Food Chem Toxicol 2013;56:398–405.

atriol-type saponins ratio of 2–3:1 and a ginsenoside Rb1-to-Rg1 ratio of 14–17:1. Higher levels of ginsenosides are *not* inherently superior in ginseng extracts, as this can start to overcome the presence of other beneficial constituents.

β-Cell Protectors and Regenerators

There are hints in the literature about a range of herbs that may work in patients with DM1 by either protecting their existing pancreatic β-cells from further destruction or bringing some of these cells back to functional status. One of the earliest reports of this effect concerned the herb *Gymnema sylvestre* (gurmar, gymnema), a vining plant native to tropical central and southern India and into tropical Africa. The leaves are used as medicine, and its Hindi name *gurmar* translates literally as "sugar destroyer." This refers to the fact that taking crude leaf, powder or liquid extracts of it directly in the mouth deadens most taste sensations, most notably those for sweets and bitter flavors.[50] The herb's Sanskrit name *meshashringi* translates as "ram's horns" and refers to the shape of its fruits (long tapered capsules, classic for plants in the Asclepiadaceae family, such as this plant).

In an animal study, giving type 1 diabetic rats two different extracts of gymnema leaf led to a doubling of the number of β-cells in their pancreases, compared to before treatment.[51] This result has been replicated independently.[52] In an open trial with 27 patients with DM1, the same water-soluble extract of gymnema leaf, at a dose of 400 mg daily, was shown to increase serum insulin levels, while lowering the patients' HgbA1c and lipid levels and reducing necessary insulin doses.[53]

It is possible that the increase in endogenous serum insulin in these patients was the result of β-cell regeneration, or to an insulin secretagogue effect (see discussion below). No other published study, including no randomized or controlled clinical trials, the current authors have been able to find has ever apparently assessed the effect of gymnema in patients with DM1.

Many clinicians, including Mona Morstein, ND, who has extensive experience working with patients with different types of diabetes, have observed that gymnema intake, regardless of the short-term (30 minutes to 4 hours) suppression of the ability to taste sweets, reduces carbohydrate craving and intake in approximately half of patients (private communication, Mesa, AZ, February 2007). Various open trials have also shown a hypolipidemic and glucose control-enhancing effect from various gymnema extracts, either alone or in formulas with other herbs.[54–56]

In mice treated with streptozotocin, a chemical that destroys β-cells, an extract of cinnamon (species not stated) proanthocyanidins protected against the development of DM1.[57] This was partially the result of inhibition of inflammatory pathways such as nuclear factor–κB and inducible nitric oxide synthase, partially by reducing oxidative stress, and partially by actually restoring β-cell levels. This suggests that cinnamon may be also be a β-cell protector and regenerator and should be considered for preventing and treating (early) DM1.

Studies in mice with STZ-induced DM1 found that American ginseng root ethanol extract increased insulin levels consistent with β-cell regeneration.[58]

Insulin Secretagogues

Insulin secretagogues are agents that stimulate β-cells to secrete more insulin. Early generation hypoglycemic, agents such as sulfonylureas (e.g., glyburide or glipizide), are insulin secretagogues. While these agents can induce a short-term benefit for lowering blood sugar, their long-term use leads to increased insulin resistance and β-cell burnout/death.[59] Other insulin secretagogues might not cause β-cell demise, but in patients with DM2, it is hard to imagine these agents not ultimately worsening underlying insulin resistance. However, some newer oral hypoglycemic agents that are potassium channel–openers instead of -closers may actually protect β-cells.[59]

Some herbs have shown worrying signs of being insulin secretagogues, with little to no research put into determining

the mechanisms behind this. In vitro and in vivo, a "high–molecular-weight" gymnema leaf extract stimulated insulin secretion by human β-cells.[60] In that same study, patients with DM2 given the same extract of gymnema had increased serum insulin and C-peptide levels, both of which are classic indicators of insulin secretagogue effects.

Other trials of gymnema and its close relative *G. montanum* in patients with DM2 showed increased serum insulin levels.[54,61] Dr. Morstein reported that she and Richard Bernstein, MD, one of the foremost diabetes physicians in the United States, have not seen an insulin secretagogue effect with the gymnema products they were using.[1] Berberine has been shown to not be an insulin secretagogue in humans.[62] Further research on medicinal plants should always include assessment for the possibility of an insulin secretagogue effect and, in particular, long-term studies are urgently needed with all herbs used in diabetes to investigate what, if any, negative long-term effects they might have.

Conclusion

There are many botanicals with a potential ability to assist treatment of diabetes. One of the most important mechanisms of action is insulin sensitization, which involves many biomolecular mechanisms. These mechanisms are just starting to be determined for both herbal constituents and pharmaceuticals. Various insulin-sensitizing herbs and their constituents, based on many clinical trials, offer a unique and safe approach to improving glycemic control.

Part 2 of this article will cover *Mormordica charantia* (bitter melon) and *Opuntia* spp. (prickly pear), along with some less well-known potential choices for helping patients cope with this all too common ailment. ■

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