Herbs for Diabetes

Update—Part 2

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Abstract

This article continues a review of herbal medicines for diabetes mellitus (DM) begun in the prior issue of this Journal. The research on *Momordica charantia* (bitter melon) fruit for diabetes mellitus (DM) published since 2005 is reviewed. Vegetable insulin derived from the seeds of bitter melon is discussed. Research on, and use of, *Opuntia* spp. (prickly pear) fruit and pad for DM since 2000 is reviewed. A thorough discussion of *Trigonella foenum-graecum* (fenugreek) seed and *Aloe vera* (aloe) gel, both relatively well-studied agents, is included.

Several less well-documented but intriguing herbal antidiabetics, including *Capparis spinosa* (capers) fruit, *Juglans regia* (English walnut) leaf, *Rauvolfia vomitoria* (African snakeroot) root, *Citrus aurantium* (bitter orange) peel, and *Salvia officinalis* (sage) leaf are reviewed.

Introduction

In part 1 of this article, various herbal remedies for diabetes mellitus (DM) were discussed, including insulin sensitizers and β-cell protectors and regenerators. Some botanicals that might have unwanted insulin secretagogue effects were also discussed. In this continuation, updated information on *Momordica charantia* (bitter melon), *Opuntia* spp. (prickly pear), *Trigonella foenum-graecum* (fenugreek), and *Aloe vera* (aloe) gel are reviewed along with a range of herbs not usually considered for patients with DM that have been the subject of clinical trials for that condition in the past few years.

Bitter Melon

M. charantia has been covered by the current author in depth previously, so the information here is intended only as an update on research on this botanical since 2005.[1] Briefly, bitter melon is a tropical member of the Cucurbitaceae (squash) family; the melon, indeed, has quite a bitter taste. Its medicinal fruit is commonly eaten as a food in Southeast Asia and China and has been shown to be hypoglycemic in food form.[2,3]

At least two animal studies suggest that bitter melon has a β-cell protective or regenerative effect.[4,5] There is preclinical evidence indicating that bitter melon is insulin sensitizing and is an α-glucosidase inhibitor.[6,7] Some of the other intriguing actions reported for bitter melon, not necessarily related to DM, are listed in Table 1, emphasizing the need to think of this herb as not just an antidiabetes agent.

The most recent meta-analysis of the efficacy and safety of bitter melon for patients with type 2 DM (DM2) found no support for bitter melon's use for this condition.[8] The four clinical trials assessed were of poor quality with high risk of bias. One of the better-quality studies assessed in this meta-analysis involved 127 Thai men and women with DM2 who were randomized to take bitter melon, in the form of 500 mg, 1 g, or 2 g of dried fruit pulp powder (standardized to 0.04%–0.05% charantin) or 1 g of metformin per day for 4 weeks.[9] Only the highest dose of bitter melon or of metformin lowered serum fructosamine levels significantly, compared to baseline; there was no significant difference between the two treatments with respect to their effects on fructosamine levels.

Since publication of this meta-analysis, one other clinical trial of better quality has been published. In it, 38 Thai men and women with DM2 were randomized to receive either 6 g of deseeded, unripe, dried fruit pulp of bitter melon daily (standardized to contain 420 mcg of charantin per capsule) or placebo for 16 weeks.[10] Serum HgbA1c and total advanced glycation endproduct (AGE) levels fell significantly in the bitter-melon group, compared to in the placebo group. No serious adverse effects occurred in either group. Diarrhea and flatulence were significantly more common in the bitter-melon group, compared to the placebo group. One open-label trial has shown that 4.8 g per day of a freeze-dried bitter melon fruit powder reduced metabolic syndrome by many measures.[11]

One problem with the research on bitter melon, as is often the case in herbal medicine, is the use of a wide variety of extracts of poorly characterized plant material.[8] Studies that have

used freeze-dried aqueous extracts cannot be reasonably compared to those using whole-plant material or ethanol extracts, particularly when the harvesting conditions of the raw material are generally unreported and any level of quality analysis is absent. Until some work is performed to develop and apply quality standards, the research results will remain conflicted and confused.

Until then, ideally, bitter melon should be incorporated into the diet in the amounts of 2–3 oz per day, as that is closest to the melon's traditional use. Given its flavor, this is a difficult recommendation for most patients to follow, so capsules of unextracted powdered fruit are recommended in a dose of at least 2 g per meal. This supplement should be used only as part of a complete program designed to address DM; and not too much should be expected from this medicinal food if it is used by itself.

A 166 amino-acid protein—known as polypeptide P or vegetable insulin (v-insulin)—isolated from bitter melon seed in the 1970s has been shown to be homologous to animal insulin.[12] When given to humans with DM, their blood sugar levels fell significantly within 60 minutes and this effect was maintained for 6 hours. Hypersensitivity reactions did not occur in this small case series.

Subcutaneous administration of polypeptide P was subsequently reported to be hypoglycemic in another small case series of patients with DM.[13] Unfortunately, it could not be confirmed if the subjects in these case series had type 1 DM or DM2. This raises the intriguing possibility of a plant-based insulin, although further clinical research on this was not identified in the literature. Only bitter melon harvested in June or July in Shanghai, China, contained polypeptide P; bitter melon harvested later did not contain this compound.[14]

Prickly Pear

Another medicinal food used for diabetes comprises various species of *Opuntia* (prickly pear cactus). The information presented here is an update to a previously published article about this traditional Southwestern American/Northern Mexican antidiabetes plant.[15] The pads (modified leaves) of prickly pear, each referred to as a *nopal* in Spanish (each fruit is called a *tuna*), are the parts used (and sometimes the fruits are used).

In all cases, the plant has to be prepared carefully to remove the very obvious spines, but also the much less obvious—but equally problematic—glochid hairs. Completely removing the outer skin while wearing gloves or using a blowtorch on the outer skin are the most reliable methods for removing the glochids.

Differences in extracts and forms of prickly pear used in research are as big an issue as they are with bitter melon. At least one study has shown that the age of the *nopal* at harvest affects its chemistry and likely its hypoglycemic effects.[16] It is most important for a patient to take prickly pear right before, or with, a meal to prevent unwanted hepatic reactions to glucose intake, as discussed below.

Three clinical trials identified were published since 2000 on prickly pear and DM and related syndromes. In one trial, a single 300-g dose of steamed *Opuntia ficus-indica* (Indian fig) *nopal* was compared to no additional treatment in 50 subjects with DM2 who consumed a high-carbohydrate breakfast.[17] Adding the *nopal* to the high-carbohydrate breakfast significantly reduced the area under the curve for total glucose exposure and insulin secretion. This suggests (and is supported by animal research cited below) that the *nopal* mainly acts by preventing acute hepatic glucose secretion in the face of a glu-

Table 1. Bitter Melon Actions Largely Unrelated to Diabetes Mellitus

Action & model	Extract	Reference
Phytoestrogen; ovariectomized rats	Fruit extract	Cevik, et al. 2015[a]
Antineoplastic; hepatocellular carcinoma cells	*Momordica charantia* lectin	Zhang, et al. 2015[b]
Immunomodulating; immunosuppressed mice	Polysaccharides	Deng, et al. 2014[c]
HIV integrase inhibition; in vitro	MAP30 protein	Lee-Huang, et al. 1995[d]
HHV-8 inhibition; in vitro	MAP30 protein	Sun, et al. 2001[e]
Vulnerary; diabetic rats	Fruit ointment (but not crude fruit powder)	Hussan, et al. 2014[f]
Antimalarial; in vitro	Ethanol extract of leaf	Olasehinde, et al. 2014[g]
Antidepressant, anxiolytic; mice	Fruit extract	Ishola, et al. 2014[h]

[a]Cevik O, Akpinar H, Oba R, et al. The effect of *Momordica charantia* intake on the estrogen receptors ESRα/ESRβ gene levels and apoptosis on uterine tissue in ovariectomy rats. Mol Biol Rep 2015;42:167–177; [b]Zhang CZ, Fang EF, Zhang HT, et al. *Momordica charantia* lectin exhibits antitumor activity towards hepatocellular carcinoma. Invest New Drugs 2015;33:1–11; [c]Deng YY, Yi Y, Zhang LF, et al. Immunomodulatory activity and partial characterisation of polysaccharides from *Momordica charantia*. Molecules 2014;19:13432–13447; [d]Lee-Huang S, Huang PL, Huang PL, et al. Inhibition of the integrase of human immunodeficiency virus (HIV) type 1 by anti-HIV plant proteins MAP30 and GAP31. Proc Natl Acad Sci U S A 1995;92:8818–8822; [e]Sun Y, Huang PL, Li JJ, et al. Anti-HIV agent MAP30 modulates the expression profile of viral and cellular genes for proliferation and apoptosis in AIDS-related lymphoma cells infected with Kaposi's sarcoma–associated virus. Biochem Biophys Res Commun 2001;287:983–994; [f]Hussan F, Teoh SL, Muhamad N, et al. *Momordica charantia* ointment accelerates diabetic wound healing and enhances transforming growth factor-β expression. J Wound Care 2014;23:400,402,404–407; [g]Olasehinde GI, Ojurongbe O, Adeyeba AO, et al. In vitro studies on the sensitivity pattern of *Plasmodium falciparum* to anti-malarial drugs and local herbal extracts. Malar J 2014;13:63; [h]Ishola IO, Akinyede AA, Sholarin AM. Antidepressant and anxiolytic properties of the methanolic extract of *Momordica charantia* Linn (Cucurbitaceae) and its mechanism of action. Drug Res (Stuttg) 2014;64:368–376.

HIV, human immunodeficiency virus; MAP, *Momordica* anti-HIV protein; HHV-8, human herpes virus 8 (Kaposi sarcoma–associated herpes virus).

cose challenge without having long-term insulin-sensitizing or other hypoglycemic effects.

One double-blinded trial randomized 68 women with metabolic syndrome to either 1.6 g of a dried aqueous extract of prickly pear *nopales* per meal or placebo for 42 days.[18] High-density lipoprotein (HDL) cholesterol levels rose significantly, compared to baseline in the prickly-pear group, while there was no change in HDL levels in the control group. By the end of the study, 39% of the prickly-pear group no longer met the criteria for metabolic syndrome, while only 8% of the placebo group had recovered. The lack of intergroup statistical comparison greatly weakened this study.

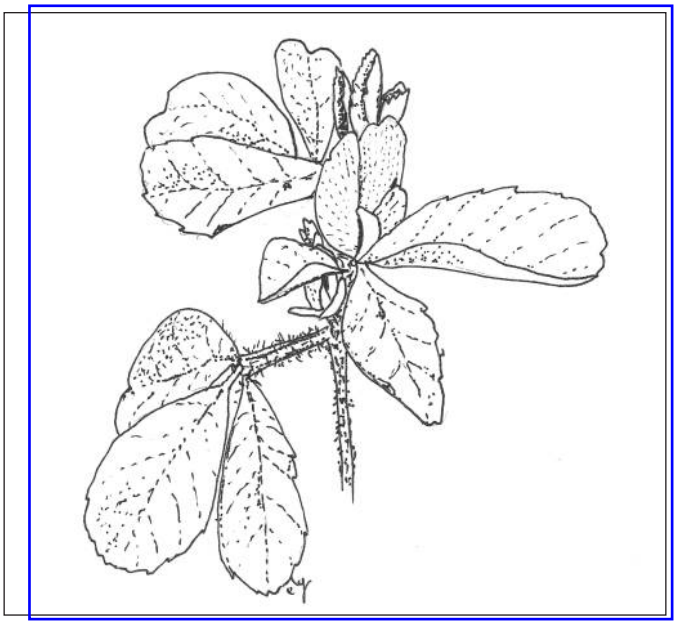
Another double-blinded trial randomized 29 men and women who were obese and had pre-DM to receive either an aqueous extract of 200 mg of *O. ficus-indica* pad and fruit skin twice daily or placebo for 16 weeks.[19] There was no significant difference between the experimental and control groups in glycemic control or lipid profiles. In the group who had received 400 mg of this extract 30 minutes before a 75-g glucose tolerance test, glucose tolerance improved significantly, compared to the group who took the test without additional intervention. This study suggests that the extract and dose used were not effective for chronic use but they were safe with no reported adverse effects.

One open trial was conducted with men who did not have DM but who did have dyslipidemia. This trial showed that adding 250 g of *Opuntia robusta* (wheel cactus) *nopal* to the men's diets significantly lowered the men's total and LDL cholesterol, triglycerides, blood glucose, insulin, and uric acid levels in their serum after 8 weeks.[20]

Various preclinical studies have been published in the past decade, which helps illuminate possible actions and mechanisms of prickly pear further. For example, the seed oil has been shown to be hypoglycemic in rats with DM, in part, by blocking glucose absorption.[21] Another example is a study in which a combination of *O. ficus-indica* grown in Korea and *Dioscorea nipponica* (Japanese wild yam, *chuan shan long*) root reduced serum lipids and insulin levels in ovariectomized mice by changing hepatic metabolism.[22]

More examples of preclinical studies include the following: Juice of the pad of *Opuntia streptacantha* (*nopal cardón*) inhibited α-glucosidase significantly in vitro.[23] A traditional cold infusion of *nopal cardón* was shown to prevent hyperglycemia by blocking hepatic glucose output, without having a persistent hypoglycemic effect, compared to controls, in diabetic rats.[24] *Opuntia dillenii* (erect prickly pear, *nopal estricto*) polysaccharides lowered blood glucose without raising serum insulin in diabetic rodents, apparently by reducing liver oxidation and protecting insulin sensitivity in peripheral tissues.[25]

Most studies with prickly pear have found it safe for moderate-term use. There is one case study suggesting that a combination of prickly pear pads, metformin, and glipizide could cause hypoglycemia.[26] Patients who are taking antidiabetic medications, including insulin, who add any of the herbs discussed in these articles should always be cautioned about the theoretical possibility of hypoglycemic episodes and instructed to monitor their blood sugar closely when the new herbs are added. In practice, this rarely happens. Dose reductions in other medications, or their elimination, are usually the goal. Patients who are currently not able, or who have shown in their histories that they are not able, to monitor their own progress closely may not be good candidates for adding new herbal medicines to their programs.



Trigonella foenum-graecum **(fenugreek). Drawing © 2015 by Eric Yarnell, ND, RH (AHG).**

Fenugreek

T. foenum-graecum seed is a common food in India and neighboring countries as well as being a traditional remedy for DM.[27] The herb's importance in the ancient Near East is attested, for example, by its presence in Tutankhamun's tomb in ancient Egypt.[28] Fenugreek is a member of the Fabaceae (pea) family. Besides being rich in fiber and containing isoflavones, the herb also has bitter-tasting alkaloids (such as trigonelline, [see Fig. 1], which has been shown to have insulin sensitizing, β-cell regenerating, hypolipidemic, neuroprotective, nootropic, and many other actions[29]). While some studies have used debitterized fenugreek, this may reduce the effectiveness of the medicine, and intact products are preferable if tolerated.

A meta-analysis of 10 randomized clinical trials of fenugreek in patients with DM was performed.[30] Overall, these trials showed that various forms of fenugreek reduced fasting plasma glucose, 2-hour postprandial glucose, and HgbA1c levels significantly, compared to placebo. The trials were generally of low methodological quality, which weakens the strength of these conclusions and raises the risk of bias.

Once again, the absence of rigorously characterized dose forms and rationales regarding dosing created great heterogeneity among the studies. Only doses > 5 g daily of fenugreek appeared to be effective for lowering blood glucose

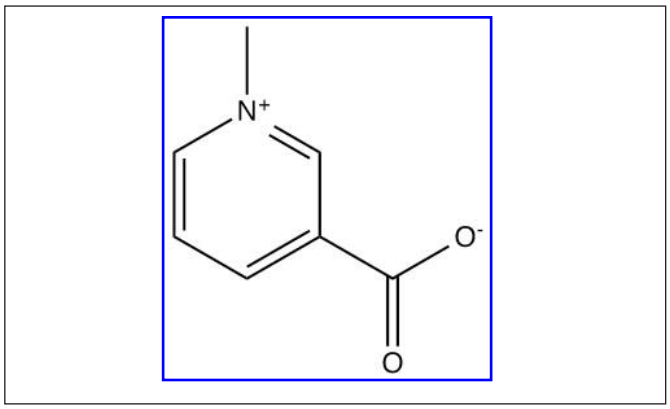


Figure 1. Trigonelline chemical structure.

levels; lower doses and hydroethanol extracts were not effective. Variations in the severity of DM between trials also created heterogeneity.[30]

Other than unusual breath and body odor and occasional digestive upset/flatulence, fenugreek rarely causes adverse effects. Fenugreek has been used safely with many oral hypoglycemic drugs as well as with insulin in clinical trials, but hypoglycemic interactions are theoretically possible when the drugs are combined with the herb.[31]

An intriguing article describes use of fenugreek mucilage to create a delayed-release form of metformin with augmented hypoglycemic activity.[32] A rabbit study found no interactions between fenugreek and the CYP3A4 substrate drugs cyclosporine and carbamazepine.[33] A study in dogs found that fenugreek significantly reduced absorption of the CYP2C19 substrate phenytoin.[34] These interaction results should be confirmed in human studies before being extrapolated clinically.

Fenugreek has been shown to have many other interesting actions, a few of which are mentioned here to emphasize that this herb is much more than just an antidiabetic and hypolipidemic herb. A separate meta-analysis of clinical trials also provided preliminary confirmation of the utility of fenugreek for correcting dyslipidemia.[35] One clinical trial found that fenugreek could restore menstrual cycles and ovulation in women with polycystic ovarian syndrome.[36]

The herb is a common traditional remedy to enhance breastmilk production, which has been validated in clinical trials.[37] A double-blinded, preliminary trial found fenugreek, compared to placebo, effective as an adjunct to L-dopa in patients with Parkinson's disease.[38]

There is some evidence that the herb can help obese patients as well as healthy young men decrease their intake of fat, which might assist weight loss or weight maintenance.[39,40] In rodents fenugreek has been shown to reduce renal calcium oxalate stones significantly.[41]

The recommended dose of fenugreek seed or seed powder is 5–25 g with each meal. If eaten with green vegetables, the meal helps mitigate the body and breath odor that can come with regular consumption of the herb, although simply accepting this odor as a sign of health may be a better solution. This inexpensive and effective medicinal food should be used more widely. Degummed seeds should not be used.

Aloe Gel

A. vera and its many close cousins in the Aloeaceae family are native to Africa but are now grown in many places in the world including, prominently, Texas. The inner portion of aloe's succulent leaves contains a mucilaginous gel with many properties, one of which is antidiabetic. This should be carefully distinguished from the opaque, white latex that can be obtained from the outermost layers of the skin of the leaves and which contains potent laxatives known as anthraquinone glycosides. Aloe gel has so many other properties it is difficult to list them all, but one of the most important additional properties relevant to diabetic populations are this herb's immunomodulating effects.[42,43]

A double-blinded trial randomized 60 patients with DM2 (which excluded trial dropouts, weakening the trial's methodological rigor) who were taking glyburide or metformin to add either a 300-mg aloe gel extract or placebo twice daily for 2 months.[44] Fasting plasma glucose, HgbA1c, total, and low-density lipoprotein (LDL) cholesterol levels all fell significantly in the aloe group, compared to the placebo group. Triglyceride and HDL cholesterol levels were not different between the groups. There were no significant adverse effects.

In another double-blinded trial, 122 obese patients with pre-DM or early DM2 were randomized to 300 mg of an aloe gel extract plus 250 mg of yeast chromone (a coumarinlike antioxidant) or placebo twice daily for 8 weeks.[45] Again, only a per-protocol statistical analysis was offered (an unfortunate weakness). Participants were not taking any other medications. Body weight, body fat percentage, and serum insulin levels fell significantly in the aloe/chromone group, compared to the placebo group. Insulin sensitivity (assessed using the standard homeostasis model of assessment—insulin resistance or homeostatic model assessment—insulin resistance [HOMA-IR]) also fell significantly in the aloe/chromone group compared to controls. This trial's results are in line with another study of dried aloe gel showing that it could improve glucose tolerance in patients with metabolic syndrome.[46]

While several other older clinical trials of aloe gel for diabetes exist, they are of significantly lower quality than those just cited and therefore are not reviewed here in any detail. They do support that aloe gel is safe in combination with older oral hypoglycemic drugs such as glyburide.[47]

The usual dose used in practice is 1–3 oz twice per day diluted with a little water if desired. Aloe gel is very safe. It should not be taken simultaneously with drugs that should be avoided with food as it could reduce their absorption.[48]

Intriguing New Antidiabetics

Many plants used in traditional medicine for DM, and some that have not been, are starting to be the subjects of clinical trials, augmenting the evidence base behind phytotherapy in

DM. Several of these are reviewed below, without attempting to be exhaustive, but rather to illustrate interesting examples and to demonstrate the potential in this field.

Caper Fruit

Capparis spinosa (caper) fruit is a Mediterranean delicacy widely used in cooking regional food. Caper has a mostly forgotten history (at least in the West) of use in patients with DM. In a double-blinded trial, 54 male and female Iranians with poorly controlled DM2 were randomly assigned to take either 400 mg of a dry, hydroethanolic extract of caper fruit or placebo three times daily for 60 days.[49] All patients continued on oral hypoglycemic medications of one kind or another. Fasting blood glucose and HgbA1c levels fell significantly in the caper group, compared to the placebo group. No significant adverse effects were observed. This provides an interesting basis for using capers to treat patients with DM (the food equivalent to the amount of extract used was 5 g) although more trials are warranted.

English Walnut Leaf

Juglans regia (English walnut) leaf is a traditional remedy for DM but has been little studied. In a double-blinded trial, 61 Iranian men and women with DM2 were randomized to take either 100 mg of an ethanol extract of English walnut leaf or placebo twice daily for 3 months.[50] Fasting plasma glucose, HgbA1c, total cholesterol, and triglyceride levels all fell significantly in the English walnut group, compared to the placebo group. There were no adverse effects.

A smaller but otherwise similar trial previously found that the extract could lower blood glucose and HgbA1c while actually raising insulin levels (a potential sign of an insulin secretagogue effect that should be viewed with trepidation).[51] English walnut leaf may work in part by inhibiting α-amylase and formation of AGEs.[52,53] A typical dose of tincture is 2–3 mL t.i.d.

In a double-blinded trial, 24 Danish adults with DM2—most of whom were taking oral hypoglycemic agents—were randomly assigned to consume 250 mL of a tea of *Rauvolfia vomitoria* (African snake root) leaf and *Citrus aurantium* (bitter orange) fruit, three times daily, or *Humulus lupulus* (hops) and lemon (placebo) tea at the same dose.[54] The African snake root/bitter orange tea is a traditional Nigerian remedy for DM. After 4 months, 2-hour postprandial plasma glucose levels fell significantly in the traditional versus the placebo tea group. HgbA1 and lipid level changes were not significantly different between the groups. This provides weak initial evidence for the potential benefits of this simple extract for helping patients with DM. There were no adverse effects. More research is warranted.

Sage Leaf

Salvia officinalis (sage) leaf has some tradition of use in DM. The first double-blinded clinical trial of sage for this indication included 80 Iranian adults with DM2 and dyslipidemia.[55] The subjects were randomly assigned to receive 500 mg of sage leaf hydroethanolic extract or placebo t.i.d. for 3 months. At the end of the trial, fasting plasma glucose, HgbA1c, total and LDL cholesterol, and triglycerides were all significantly lower in the sage group, compared to the placebo group. HDL cholesterol levels were significantly higher in the sage versus the placebo group. No adverse effects occurred.

Combined with other clinical trial evidence supporting the hypolipidemic effects of sage, it looks promising for helping patients with DM and dyslipidemia.[56] A typical dose of the tea is 3–5 g (1 tbsp) of herb per cup (200 mL) of hot water steeped for 15 minutes; 3 cups per day are consumed. A typical dose of tincture is 2–3 mL t.i.d.

Conclusion

The number of traditional herbal remedies for DM is vast. Only a small number of these have been researched to any significant extent, but this is changing. Some of the better-studied remedies, including bitter melon, prickly pear, fenugreek, and aloe gel, can be tried comfortably and safely in patients as part of antidiabetic programs. Patients who are simultaneously taking hypoglycemic medications or using insulin should be monitored to reduce the already low risk of causing excessively low blood sugar levels.

Many other herbs need to be studied further, but are safe, novel options for patients with DM. These herbs include relatively common foods and spices, such as capers and sage, as well as some more exotic herbs, such as African snakeroot. The potential for herbs to help patients with DM is substantial and deserves better-quality and more-focused research as well as wider clinical use. ■

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