REVIEW ARTICLE

Traditional Plant Medicines as Treatments for Diabetes

Clifford J. Bailey, PhD
Caroline Day, PhD

More than 400 traditional plant treatments for diabetes mellitus have been recorded, but only a small number of these have received scientific and medical evaluation to assess their efficacy. Traditional treatments have mostly disappeared in occidental societies, but some are prescribed by practitioners of alternative medicine or taken by patients as supplements to conventional therapy. However, plant remedies are the mainstay of treatment in underdeveloped regions. A hypoglycemic action from some treatments has been confirmed in animal models and non-insulin-dependent diabetic patients, and various hypoglycemic compounds have been identified. A botanical substitute for insulin seems unlikely, but traditional treatments may provide valuable clues for the development of new oral hypoglycemic agents and simple dietary adjuncts. *Diabetes Care* 12:553–64, 1989

The earliest recorded treatments for diabetes mellitus involved the use of plants. The Papyrus Ebers of 1550 BC recommended a high-fiber diet of wheat grains and ochre (1). A multitude of herbs, spices, and other plant materials have been described for the treatment of diabetes throughout the world (2–7). Since the availability of insulin, folklore medicines for diabetes have almost disappeared in occidental societies, although they continue to be the cornerstone of therapy in underdeveloped regions. Renewed attention to alternative medicines and natural therapies has stimulated a new wave of research interest in traditional practices, and the World Health Organization expert committee on diabetes has listed as one of its recommendations that traditional methods of treatment for diabetes should be further investigated (8,9).

Traditional antidiabetic plants might provide a useful source of new oral hypoglycemic compounds for development as pharmaceutical entities, or as simple dietary adjuncts to existing therapies. Sulfonylureas and metformin are valuable treatments for hyperglycemia in non-insulin-dependent diabetes mellitus (NIDDM), but they are often unable to lower glucose concentrations to within the normal range, or to reinstate a normal pattern of glucose homeostasis (10–12). Use of these therapies is restricted by their pharmacokinetic properties, secondary failure rates, and accompanying side effects (11–13). Whereas their modes of action partially compensate for the metabolic disturbances in diabetic states, they do not necessarily correct the fundamental biochemical lesions (14). Even insulin therapy does not reinstate a normal pattern of glucose homeostasis in most NIDDM patients, and overvigorous insulin treatment may carry an increased risk of atherogenesis and hypoglycemia (13,15–17). Although an orally active botanical substitute for insulin seems unlikely, new molecules to stimulate endogenous insulin biosynthesis and secretion (and to promote insulin action) are realistic possibilities. This review considers the current status of scientific and medical research in the use of traditional plant treatments for diabetes mellitus.

TRADITIONAL ANTIDIABETIC PLANTS

More than 400 different plants and plant extracts have been described as reputedly beneficial for the diabetic patient. Most of these plants have been claimed to pos-

From the Diabetes Research Unit, Biology Division, Department of Pharmaceutical Sciences, Aston University, Birmingham, United Kingdom.

Address correspondence and reprint requests to C. J. Bailey, PhD, Diabetes Research Unit, Biology Division, Department of Pharmaceutical Sciences, Aston University, Birmingham B4 7ET, UK.

sess hypoglycemic properties but most claims are anecdotal and few have received adequate medical or scientific evaluation. Those that have been evaluated may be grouped into three categories: *1*) plants from which a reputedly hypoglycemic compound or partially characterized hypoglycemic fraction has been prepared; *2*) plants reported to exert a hypoglycemic effect, but the nature of the active principle is unestablished; and *3*) plants that reputedly exert a hypoglycemic effect, but the scientific evidence is equivocal. These categories exclude the numerous traditional plants for which an independent scientific or medical evaluation has not been published.

HYPOGLYCEMIC AGENTS FROM PLANTS

Appendix 1 lists traditional antidiabetic plant treatments from which a purportedly hypoglycemic compound or fraction has been obtained. Various molecular species with hypoglycemic activity have been identified, particularly alkaloids, glycosides, and polysaccharides.

Raw onion bulbs (*Allium cepa*) and garlic cloves (*Allium sativum*) have long been used as dietary supplements for the traditional treatment of diabetes in Asia, Europe, and the Middle East (18). Concentrated extracts from the plant organs exerted a weak hypoglycemic effect in healthy and alloxan-induced diabetic animals and healthy humans (19–22). In these studies, fasting glucose concentrations were lowered and oral glucose tolerance was improved by 7–18% within 1–2 h after oral administration of aqueous and ethanolic extracts of onion and garlic at doses of ~10 g extract/kg body wt. This effect has been attributed to the volatile oils allylpropyldisulfide and diallyldisulfide oxide, excessive amounts of which can have detrimental effects on hepatic metabolism (20,23). *Allium* species are not effective in pancreatectomized or severely streptozocin-induced diabetic animals, and an insulin-releasing effect is unlikely, leaving open speculation that disulfides might retard insulin degradation or facilitate insulin action (20,22,24,25). The claim that diphenylamine is a hypoglycemic principle in onion has not been substantiated (22,26).

Several plants are deemed to contain hypoglycemic alkaloids. Leaf infusions and decoctions of *Catharanthus roseus* (periwinkle) are widely used as a traditional treatment for NIDDM. (An infusion is prepared by submerging the plant or plant organ in either cold or boiling water and allowing to stand. A decoction is prepared by submerging the plant or plant organ in cold water which is then boiled and simmered. After heat is withdrawn, the material is allowed to infuse.) Chronic administration of aqueous leaf extracts did not affect glucose homeostasis in healthy and streptozocin-induced diabetic mice (24). However, many major alkaloids isolated from this plant, including leurosine, vindoline, vindolinine, and catharanthine, exhibited a mild hypoglycemic effect within 2–5 h in healthy rats, but none was sufficiently potent to encourage further investigation (27,28). Further deterrents were the cytotoxic and neurological effects of *Catharanthus* alkaloids and the increased risk of infection, which appear to have been unappreciated or disregarded by traditional users of the plant.

Traditional use of leaves from *Tecoma stans* for the treatment of NIDDM patients has been supported by the isolation of two hypoglycemic alkaloids, tecomine and tecostanine. These alkaloids exerted a rapid (within 2 h) hypoglycemic effect when administered intravenously to healthy and alloxan-induced diabetic rabbits but were ineffective in pancreatectomized rabbits (29,30). The alkaloids showed poor stability and were required in sufficiently large doses to question their clinical potential. Seeds of *Lupinus termis* (lupin) used by Yemenite Jews have been reported to yield a fraction rich in quinolizidine alkaloids, which exerted a brief glucose-lowering effect in alloxan-induced diabetic rats but not healthy rats (2,31). The seeds of *Trigonella foenumgraecum* (fenugreek) are more widely recommended for NIDDM patients. These seeds exerted a modest and transient hypoglycemic effect in several studies with healthy and mildly diabetic animals but were not effective in severely diabetic animals (2,24,31–34). The hypoglycemic activity has been attributed to an uncharacterized alkaloid termed *trigonelline*, although other possible hypoglycemic agents such as nicotinic acid have been isolated from the seeds (31,32). There is no evidence that fenugreek seeds increase insulin secretion, but chronic administration of a defatted fraction of the seeds reduced glucagon and somatostatin concentrations in healthy dogs (24,33,35). The high fiber content of the seeds (50–60%) might also contribute to a beneficial effect in diabetic patients (35).

The antihyperglycemic effect of *Coccinia indica* (ivy gourd) has been demonstrated in a double-blind trial with NIDDM patients (36). Consumption of 6 tablets/day (dose unspecified) prepared from the homogenized and freeze-dried leaves of *C. indica* decreased basal glucose concentrations by ~20% and similarly improved oral glucose tolerance after 6 wk. Aqueous and ethanolic root extracts of *C. indica* decreased glucose concentrations by >50% when administered to healthy rabbits at a dose of 1.25 g/kg, and an uncharacterized alkaloid has been implicated as an active principle (2,37).

Cultivated fruits of *Momordica charantia* (karela) are widely used to treat diabetes in Asia and Australasia. Despite their characteristically bitter taste, they are considered to have prophylactic properties and are often included in the diet (38). In India and China, karela is crushed and dried to form tablets (39,40). Aerial parts of a wild variety of *M. charantia* (cerasee) are prepared as a decoction in Central America for the same purpose (41). Asian and West Indian immigrants have recently introduced karela and cerasee into Europe as adjuncts and alternatives to conventional treatments for NIDDM (38). Consumption of 50 ml of an aqueous extract of

karela with a 50-g oral glucose challenge reduced glucose concentrations of NIDDM patients by ~20% within 1 h (42). A similar improvement in glycemic control was noted after 2–3 mo of daily consumption of karela (42,43). Hypoglycemic effects of raw karela and aqueous karela extracts have also been reported in healthy and alloxan-induced diabetic animals (42,44,45). Oral consumption of karela does not enhance insulin release, although an aqueous extract of karela has been shown to stimulate insulin release from normal isolated islets in vitro (42,46). Unpublished studies from our laboratory indicate that karela inhibits hepatic gluconeogenesis. Decreased intestinal glucose uptake has also been reported, although we have noted that karela improved oral and intraperitoneal glucose tolerance to a similar extent (47). It has been claimed that karela contains an insulinlike peptide that lowers glucose concentrations when injected subcutaneously into insulin-dependent diabetes mellitus (IDDM) patients, but this is unlikely to account for the oral hypoglycemic effect of karela in NIDDM (48). Another purportedly hypoglycemic fraction isolated from karela and called charantin is a mixture of glycosides, mainly β-sitosterol-D-glucoside and stigmadine glucoside (49). Our laboratory has been unable to substantiate the hypoglycemic activity of these glycosides. Fractionation of karela has indicated at least two orally active hypoglycemic principles: an uncharacterized rapidly effective substance, and a slowly acting material that is present in an alkaloid-rich fraction. Note that large quantities of karela extract induced testicular lesions in dogs, and hepatic portal inflammation has been anecdotally ascribed to excessive consumption of cerasee (50).

Various glycoside-containing fractions have been implicated as hypoglycemic constituents of traditional antidiabetic plants. *Momordica foetida*, a remedy used mainly in West Africa, exerted a mild hypoglycemic effect in healthy rabbits (51). *M. foetida*, like karela, contains the glycoside fraction charantin. In the sixth century BC, the Indian physician Sushruta prescribed a mixture of plants for diabetic patients, including *Gymnema sylecvestre* (gurmar) (52). Gurmar is still used as a treatment for NIDDM patients in Asia and has been studied in healthy and alloxan-induced diabetic rabbits (2,52,53). Gurmar appeared to act in part by increasing insulin release and was ineffective in pancreatectomized animals (53). The hypoglycemic effect was slowly generated and sustained and has been attributed to an uncharacterized glycoside (2). In alloxan-induced diabetic rabbits consuming 250 mg · kg^{-1} · day^{-1} dried powdered leaves, glucose concentrations were halved after 24 wk, glycogenesis and protein anabolism were improved, and the activity of insulin-dependent enzymes such as hexokinase and glycogen synthase was increased (52). Serum enzymes and histological observations suggested reduced tissue damage in diabetic animals treated with gurmar, but clinical accounts have noted that this plant can reduce or abolish the taste sensations of sweetness and bitterness.

Leaves of *Vaccinium myrtillus* (bilberry) were widely used as a treatment for diabetes before the availability of insulin, and an active glycoside principle (neomyrtillin) was extracted (54). The active extract was reputedly effective in reducing glycosuria and postprandial hyperglycemia in most adult-onset diabetic patients but was seldom effective in juvenile-onset patients. The extract was found to enhance the hypoglycemic action of exogenous insulin and reduced insulin requirements, fostering the view that the extract might facilitate insulin action (54,55). *V. myrtillus* extracts are anecdotally claimed to be well tolerated and did not produce any obvious adverse side effects during chronic administration.

An aqueous extract of stem bark from *Ficus benghalensis* (banyan tree), used traditionally in Asia, contains a flavonoid glycoside termed *bengalenoside* (2). This produced a mild hypoglycemic effect in healthy and alloxan-induced diabetic rodents (2,56). *Ficus* extracts were not effective in pancreatectomized animals, and modest doses were toxic in some species.

Cyamopsis tetragonolobus (Indian cluster bean) is recognized in Asian folklore as a useful aid for the diabetic subject (57). Seeds of this plant are the source of galactomannan gum (guar that is used as a bulking agent for foods and cosmetics) (58). The viscosity effect of guar is exploited as a dietary adjunct to delay the rate of glucose absorption and thereby helps to reduce postprandial hyperglycemia (59). In addition to the guar seeds, the pods of the Indian cluster bean are also believed to contain an antidiabetic principle (57). Closely related and similarly effective to guar gum is the polysaccharide glucomannan, which was isolated from tubers of *Amorphophallus konjac* (konjac plant) (60). This is a traditional Japanese aid for diabetes. The efficacy, mode of action, and precautions associated with the use of guar and other dietary fiber supplements have recently been reviewed (61).

Several antidiabetic treatments from the Orient have recently been shown to contain antihyperglycemic polysaccharides and peptidoglycans (i.e., *Aconitum carmichaeli*, *Anemarrhena asphodeloides*, *Atractylodes japonica*, *Dioscorea japonica*, *Eleutherococcus senticosus*, *Ephedra distachya*, *Ganoderma lucidum*, *Lithospermum erythrorhizon*, *Oryza sativa*, *Panax ginseng*, *Panax quinquefolium*, and *Saccharum officinarum*) (62–73). At doses up to 100 mg/kg body wt, the principles from these plants lowered glucose concentrations in healthy and alloxan-induced diabetic mice within 7 h. The most common polysaccharide or peptidoglycan principle from each plant reduced glucose concentrations by >20% in the alloxanized mice, and the hypoglycemic effect was often still in evidence after 24 h. Because the principles were effective after intraperitoneal administration, it has been suggested that their mode of action is different than the intestinal fiber effect of guar and glucomannan. Although the plants are known to contain other extracts with different pharmacological effects (e.g., central nervous system stimulation and hypertensive effects of

ephedrine from *Ephedra* species and central nervous system stimulation by *Panax* species), the toxicology of the polysaccharide and peptidoglycan principles has not been reported.

Another group of hypoglycemic principles is the hypoglycins (aminopropylpropionic acid derivatives isolated from the unripe fruits of *Blighia sapida* [ackee fruit]), a traditional treatment for diabetes in Central America and Africa (28,74). Hypoglycins are effective in healthy and diabetic animals and humans, promoting glucose use and inhibiting gluconeogenesis secondary to the inhibition of long-chain fatty acid oxidation (74,75). However, their toxic effects have precluded further development. The unripe fruits of *B. sapida* are well recognized to induce neuroglycopenia if consumed by fasting individuals, but awareness of the risk has not prevented excessive fatality (74). Children are especially susceptible, presenting with listlessness, nausea, and convulsions, the so-called vomiting sickness of the West Indies.

The traditional use of *Galega officinalis* (goat's rue or French lilac) in medieval Europe is explained by its rich content of the hypoglycemic substance guanidine (4,76,77). Although guanidine proved too toxic for clinical use, the alkyl diguanides synthalin A and synthalin B were introduced as oral antidiabetic agents in Europe in the 1920s but were discontinued when insulin became more widely available. Experience with guanidine and diguanides prompted the development of biguanides and the current use of metformin (78,79). The guanidine-rich plant *Ilex guayusa* is still used as a treatment for diabetes by the Amaguajes Indians of South America, and an aqueous extract from the leaves of this plant is also used by modern druids (24). This extract has been shown to retard the development of streptozocin-induced diabetes in mice (24).

Some antidiabetic plants used in underdeveloped regions may be helpful for nonclassical types of diabetes such as tropical pancreatic diabetes, type J, type K, and other forms of malnutrition diabetes (80,81). For example, *Poterium spinosum* is an ion-rich antidiabetic plant used by nomadic Bedouins in desert regions of the Middle East (82). Consumption of a root infusion for 1–2 mo is reported to eliminate symptoms of diabetes for at least 1 yr (83). Traditional use of an infusion of *Medicago sativa* (alfalfa) leaves in South Africa may be associated with the high manganese content of this plant (84). Manganese chloride has been shown to exert a hypoglycemic action in an IDDM patient, and manganese is now recognized as a necessary cofactor for ATP phosphorylation of the β-subunit of the insulin receptor (84,85). An antidiabetic effect of alfalfa, which has been substantiated in streptozocin-induced diabetic mice, might also be associated with the plant's high concentration of vitamin K (86). The synthetic analogue vitamin K_5 can acutely mimic certain actions of insulin (87). Widespread use of *Saccharomyces cerivisae* (yeast) as a traditional treatment for diabetes may be correcting deficiencies of vitamin B complexes or chromium. Chromium deficiency has been implicated as a contributory cause of insulin resistance in certain types of diabetes, and chromium is believed to be the so-called glucose tolerance factor in yeast (80,88–90).

Coleus forskohlii does not appear to have been used as a traditional treatment for diabetes, but the diterpene forskolin from this plant stimulates glucose-induced insulin secretion in vitro (91). This appears to reflect a general stimulatory influence of forskolin on adenylate cyclase activity, obviating its specific suitability as an antidiabetic treatment (92).

PLANTS WITH UNCHARACTERIZED HYPOGLYCEMIC PRINCIPLES

Appendix 2 lists a selection of traditional antidiabetic plants with scientific and/or medical support for a hypoglycemic effect, although the active principles are unestablished.

Agaricus bisporus (common edible mushroom) is considered a useful dietary adjunct for diabetes in Europe, and a hypoglycemic effect has been shown in streptozocin-induced diabetic mice (24). *A. bisporus* consumption improved insulin sensitivity in diabetic mice, and a lectin from this mushroom stimulated insulin release by isolated islets of healthy rats (24,93,94). Other mushrooms used traditionally in Europe include *Amanita phalloides* (stinking amanita), which lowered glucose concentrations in healthy subjects, and *Coprinus comatus* (ink cap or lawyer's wig), which also lowered glucose concentrations in healthy rats and mice (95–98). The poisonous effect of *A. phalloides* is probably due to neuroglycopenia after hepatic glycogen depletion and hepatic necrosis (95,96). Other noncultivated traditional antidiabetic mushrooms such as *C. comatus* can accumulate heavy metals with toxic consequences if consumed in excess.

Consumption of several plant remedies reduced the rate of development and the extent of hyperglycemia in streptozocin-induced diabetic mice: leaves of *Agrimonia eupatoria* (agrimony) and *Eucalyptus globulus* (eucalyptus), seeds of *Coriandrum sativum* (coriander), and berries of *Juniperus communis* (juniper) (86). Leaves of *Rubus fructicosus* (blackberry) were effective in alloxan-induced diabetic rats but not in streptozocin-induced diabetic mice (86,99). The traditional use of *Cassia alata*, *Cuminum nigram*, *Lavandula stoechas*, *Salvia lavandulifolia*, and *Szygium jambolana* (java plum) has been supported by studies in alloxan-induced diabetic rats and rabbits, but their mode of action is unestablished (100–103,133). An aqueous extract of stems of *Opuntia streptacantha* reduced basal glucose concentrations in NIDDM patients and alloxan-induced diabetic rabbits, but not in nondiabetic humans and healthy rodents (104,105). In NIDDM patients, an 18% reduction in glucose concentrations was observed 3 h after ingestion of 500 g of the extract. This was accompanied

by a 50% fall in insulin concentrations, indicating that this treatment is likely to exert an extrapancreatic action (105).

Lythrum salicaria (willowstrife) was effective in healthy rabbits and was associated with a doubling of insulin concentrations by 4 h (106). *Tinospora crispa* also appeared to act by increasing insulin concentrations (107). An aqueous extract of this plant exerted a direct stimulatory effect on insulin release by cultured islet β-cells. *Phaseolus vulgaris* (harriot bean) was used before the availability of insulin. An aqueous extract from the pods, termed *phaseolan*, showed hypoglycemic activity in alloxan-induced diabetic rats and rabbits (99,108).

Old-fashioned vegetable diets are now recognized as a valuable source of fiber-rich complex carbohydrates (109). Their retarding effect on the rate of intestinal glucose absorption may account for early claims of an antihyperglycemic effect. However, several traditionally recommended vegetables, notably leaves of *Brassica oleracea* (cabbage) and *Letuca sativa* (lettuce), tubers of *Solanum tuberosum* (potato), and roots of *Brassica rapa* (turnip) have been claimed to yield nonfibrous hypoglycemic extracts, some of which lowered glucose concentrations after parenteral administration (28,99,110). The styles of *Zea mays* (maize), which are traditionally advocated for diabetes in Europe, Africa, and the Americas, have been shown to contain a mineral-rich fraction with hypoglycemic activity in rabbits (27,111). Maize contains a high content of indoleacetic acid (IAA), which has been debated as a possible hypoglycemic agent (112). However, modest doses of IAA, gibberellic acid, and abscisic acid did not exhibit a hypoglycemic effect in healthy rats and mice, and only IAA significantly lowered glucose concentrations at doses that can be toxic with repeated administration (unpublished observations).

An herbal preparation from Kuwait, containing equal portions of *Nigella sativa*, *Commophora molmol*, *Aloe vera* (Mediterranean aloe), gum arabic, and gum asafoetida, has been reported to reduce glycemia in healthy and streptozocin-induced diabetic rats without altering insulin concentrations (113). *Aloe vera* is claimed to contain several polysaccharides that are hypoglycemic in mice, and chronic ingestion of dried sap from this plant lowered glucose concentrations in alloxan-induced diabetic mice and NIDDM patients (114,115).

PLANTS WITH EQUIVOCAL ACTIVITY

In North America, an alkaloid extract from *Ruta graveolens* (rue) rutin has been recommended for diabetes, but its efficacy is unconfirmed (39). *R. graveolens* is added in trace amounts to foods and beverages as a flavoring, although large amounts are narcotic, irritating to skin, arbortifacient, and contraindicated in pregnancy. Rutin has been ascribed beneficial effects in patients with cardiovascular and thrombotic disorders in addition to diabetes, but its mode of action is uncertain. Also recommended for diabetes in North America is a leaf extract of *Artemesia dracunculus* (tarragon) which contains rutin (39). In Europe, a tea from the leaves of *Polygonum aviculare* (knotgrass) and various black and green teas used in the Middle East have been ascribed hypoglycemic properties, but these await scientific evaluation (26,39). Xiaoke tea, an infusion of unclassified dried leaves from China, reduced glucose concentrations in streptozocin-induced diabetic mice without affecting insulin concentrations but was ineffective in diabetic BB rats (116,117). An Indian preparation of crushed dried herbs (bhadraprash) has received a reputation as a treatment for diabetes, but a consistent effect was not observed in streptozocin-induced diabetic mice (118).

Several plants that are traditionally used for the treatment of diabetes exerted little or no effect on glycemic control during recent studies in streptozocin-induced diabetic mice (i.e., *Anacardium occidentale* [cashew], *Taraxacum officinale* [dandelion], *Sambucus nigra* [elder], *Humulus lupulus* [hops], *Salvia officinale* [sage], *Daucus carrota* [wild carrot], *Glycyrhizza glabra* [liquorice], *Chelidonium majus* [celandine], *Alchemilla vulgaris* [lady's mantle], and *Convallaria majalis* [lily of the valley]) (24,86). However, absence of an effect in one condition of diabetes does not exclude the possibility of an effect on glycemia in other types of diabetes or a beneficial effect other than glycemic control. The traditional antidiabetic plants *Arctium lappa* (burdock) and *Urtica dioica* (nettle) actually increased hyperglycemia in streptozocin-induced diabetic mice (24). Indeed, it has been suggested that some traditional antidiabetic plants (e.g., hops) may contain both hypo- and hyperglycemic principles, with the different effects predominating at different times and to different extents in different types of diabetes (28).

There have been anecdotal claims and conference reports that certain Asian and South American antidiabetic plants can obviate the need for insulin in reputedly IDDM patients. However, the total absence of endogenous insulin (C-peptide negative) was not established, and the design and assessment of the studies must be questioned. An aqueous extract from the heartwood of *Pterocarpus marsupium* (false teak), which is traditionally recommended in Asia for NIDDM, has been reported as effective in the treatment of NIDDM (119,120). Epicatechin, a flavonoid from *P. marsupium*, has also been claimed to promote β-cell regeneration and alleviate hyperglycemia in alloxan-induced diabetic rodents (121,122). Although epicatechin can enhance insulin release from healthy rat islets in vitro, the antidiabetic and regenerating effects have not been substantiated in recent studies (123–126). Concentrated aqueous extracts of *P. marsupium* and epicatechin exerted no effect on glycemic control in streptozocin-induced diabetic rats and mice or BB rats (118,127). An extract prepared from the young leaves of *Phyllanthus sellowianus* (serando blanco), used traditionally in India

TABLE 1
Antidiabetic plants traditionally considered as efficacious in treatment of diabetes-associated complications

Complications	Plants
Polydipsia	*Panax ginseng, Polygonatum humile, Polygonatum macropodum, Polygonatum officinale*
Emaciation	*Allium sativum, Cichorum intybus*
Atherosclerosis	*Allium cepa, Allium sativum, Lycium chinensis, Panax ginseng, Taraxacum officinale, Trigonella foenumgraecum*
Retinopathy	*Daucus carrota, Lycium chinensis, Taraxacum officinale, Vaccinium myrtillus*
Nephropathy	*Lycium chinensis*
Impotence	*Ceiba petandra, Coriandrum sativum, Crocus sativa, Panax ginseng, Papaver somniferum*

Table compiled from traditional and anecdotal sources. Controlled clinical studies have not been undertaken to support these claims.

and the South American pampas, has been ascribed lasting curative properties. Specimens of *P. sellowianus* are rare, and chronic studies have not been undertaken.

Most traditional plant treatments for diabetes are used in remote regions of the world. Difficulties in obtaining pukka specimens and discrepancies over classification have hampered their scientific evaluation. There are many anecdotal reports awaiting investigation. However, secrecy surrounding the use of plant remedies, the reluctance of traditional practitioners to disclose the contents of their preparations and sources of information, plus the frequent transfer of knowledge by the verbal route alone have made documentation difficult. Indeed, some traditional knowledge is undoubtedly lost with the encroachment of Western practices into remote regions, and the disappearance of certain environments such as rain forests may eliminate the opportunity to obtain and study indigenous plants (128).

DIABETIC COMPLICATIONS

It is possible that some traditional treatments for diabetes may create a feeling of improved well-being without necessarily reducing hyperglycemia. There have been unsubstantiated claims that certain plants can ameliorate complications of diabetes (Table 1), but the objective assessment of complications is difficult and the placebo effect of natural remedies cannot be discounted. No controlled studies of microvascular, macrovascular, or neuropathic complications have been undertaken with traditional therapies. A plant that is thirst quenching or increases sympathetic tone might gain a traditional reputation as efficacious without providing any long-term benefits to the underlying malady. Members of the *Allium* family, particularly garlic, are traditionally considered to give strength and combat arterial vascular disease (18). Garlic reduces polydipsia and weight loss in severely streptozocin-induced diabetic mice without improving glycemic control (86). Onion has been reported to lower free fatty acid concentrations in healthy subjects, and seeds of *T. foenumgraecum* (fenugreek) reduced cholesterol levels in diabetic dogs (20,129). Other traditional antidiabetic plants have been anecdotally claimed to possess hypolipidemic properties.

SIDE EFFECTS

Little toxicological information exists concerning traditional antidiabetic plants. Use of the plants over many centuries and sometimes as regular constituents of the diet might be expected to reveal any obviously detrimental side effects through the cumulative knowledge of personal experiences. Nevertheless, patients are prone to overindulge in natural treatments, believing their efficacious reputation to imply safety. The major known toxic effects of plants considered in this review have already been mentioned, but chronic consumption of large amounts of traditional remedies must always be regarded with caution. A study in South Africa recorded cases of fatal hypoglycemia after consumption of unspecified herbal medicines and commonly found this to be associated with hepatic and renal necrosis (130).

A case-study report noted that the hypoglycemic effect of *M. charantia* was additive to that of chlorpropamide, and *V. myrtillus* and synthalin apparently reduced insulin requirements (54,55,131). Possible interactions of traditional and conventional therapies have otherwise been neglected.

CONCLUSION

Diabetes is possibly the world's fastest growing metabolic disease, and as knowledge of the heterogeneity of this disorder increases, so does the need for more appropriate therapies (132). Traditional plant medicines are used throughout the world for a range of diabetic presentations. The study of such medicines might offer a natural key to unlock a diabetologist's pharmacy for the future.

APPENDIX 1
Proposed hypoglycemic agents from traditional antidiabetic plants

Plants	Location of use	Active part of plant	Active substance	Activity demonstrated	Refs.
Aconitum carmichaeli	Orient	Root	Aconitan A (polysaccharide)	Diabetic mice	62
Allium cepa	Asia, Europe, Middle East	Bulb	Alkyldisulfides	Diabetic rabbits	23
Allium sativum	Asia, Europe, Middle East	Bulb	Alkyldisulfides	Healthy rabbits	19
Amorphophallus konjac	Orient	Tuber	Glucomannan (polysaccharide)	IDDM and NIDDM patients	60
Anemarrhena asphodeloides	Orient	Rhizome	Anemaran A (polysaccharide)	Diabetic mice	63
Atractylodes japonica	Orient	Rhizome	Atractan A (polysaccharide)	Diabetic mice	64
Blighia sapida	Africa, Central America	Fruit (unripe)	Hypoglycins (aminopropyl-propionic acid derivatives)	IDDM and NIDDM patients	74
Catharanthus roseus	Africa, Asia, Europe, Australasia	Leaf	Alkaloids	Healthy rats	27,28
Coccinia indica	Asia	Leaf	Uncharacterized alkaloids	NIDDM patients	36
Cyamopsis tetragonolobus	Asia	Seed and pod	Galatomannan (polysaccharide)	IDDM and NIDDM patients	57,59
Dioscorea japonica	Orient	Rhizophor	Dioscoran C (polysaccharide)	Diabetic mice	65
Eleutherococcus senticosus	Orient	Root	Eleutherans (polysaccharides)	Diabetic mice	66
Emericella quadrilineata	Asia	Fruit body	Aminobutyric acid derivative	Diabetic mice	139
Ephedra distachya	Orient	Aerial	Ephedran A (polysaccharide)	Diabetic mice	67
Ficus bengalensis	Asia	Stem bark	Uncharacterized glycoside	Healthy rodents	56
Galega officinalis	Europe	Leaf	Guanidine	NIDDM patients	78
Ganoderma lucidum	Orient	Fruit body	Ganoderan A (polysaccharide)	Diabetic mice	68
Gymnema sylvestre	Asia, South Africa	Leaf	Uncharacterized glycoside	Diabetic rabbits	52
Lithospermum erythrorhizon	Orient	Root	Lithosperman B (polysaccharide)	Diabetic mice	69
Lupinus termis	Middle East	Seed	Quinolizidine alkaloids	Diabetic rats	31
Momordica charantia	Asia, Australasia, Central America, West Africa	Aerial	Uncharacterized glycosides and alkaloids*	NIDDM patients	42
Momordica foetida	West Africa	Aerial	Uncharacterized glycosides	NIDDM patients	51
Oryza sativa	Orient	Root	Oryzarans (polysaccharides)	Diabetic mice	70
Panax ginseng	Orient	Root	Panaxans (polysaccharides)	Diabetic mice	58
Panax quinquefolium	Orient	Root	Quinquefolans (polysaccharides)	Diabetic mice	72
Saccharum officinarum	Orient	Stalk	Saccharan C (polysaccharide)	Diabetic mice	73
Tecoma stans	Central and South America, Middle East, West Africa	Leaf	Characterized alkaloids	Diabetic rabbits	29,30
Trigonella foenumgraecum	Asia, Europe	Seed	Trigonelline (alkaloid)	Diabetic animals	31
Vaccinium myrtillus	Europe, North America	Leaf	Neomyrtillin (glycoside)	Diabetic humans	54

Table based on previous publication by authors (3). IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.
*Authors' unpublished observations.

APPENDIX 2
Traditional antidiabetic plants with hypoglycemic effects

Plants	Location of use	Active part of plant	Activity demonstrated	Refs.
Agaricus bisporus	Europe	Fruit body	Diabetic mice	24
Agrimonia eupatoria	Europe	Leaf	Diabetic mice	86
Aloe vera	Middle East	Aerial	Diabetic humans and mice	115
Amanita phalloides	Europe	Fruit body	Healthy humans	95
Artemisia abbysinica	Middle East	Aerial	Diabetic mice	140
Cassia alata	Asia	Leaf	Diabetic rats	133
Coprinus comatus	Europe	Fruit body	Healthy rats and mice	97,98
Coriandrum sativum	Asia	Seed	Diabetic rats and mice	99
Cuminum nigram	Asia	Seed	Diabetic rabbits	100
Eucalyptus globulus	Africa, South America	Leaf	Diabetic mice	86
Hammada salicornia	Middle East	Aerial	Diabetic mice	134
Juniperus communis	Europe	Fruit	Diabetic mice	86
Lavandula stoechas	Europe	Leaf	Diabetic rats	103
Lythrum salicaria	Europe	Aerial	Healthy rabbits	106
Melia azadirachta	Asia, Middle East	Seed	Diabetic rats	135
Opuntia streptacantha	Central America	Stem	Diabetic humans and rabbits	104,105
Phaseolus vulgaris	Europe	Pods	Diabetic rats and rabbits	99,108
Quercus infectoria	Asia	Fruit	Healthy rabbits	136
Rubus fructicosus	Europe	Leaf	Diabetic rats	99
Salvadora persica	Middle East	Aerial	Healthy mice	137
Salvia lavandulifolia	Central America	Flower	Diabetic rabbits	101
Syzygium jambolana	Asia, Europe	Fruit	Diabetic rabbits	102
Teucrium oliverianum	Middle East	Aerial	Diabetic mice	138
Tinospora crispa	Asia	Aerial	Diabetic rats	107

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