

Role of Selected Indian Plants in Management of Type 2 Diabetes: A Review

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ABSTRACT

Type 2 diabetes has become a global epidemic. Modern medicines, despite offering a variety of effective treatment options, can have several adverse effects. Ayurveda, a science that uses herbal medicines extensively, originated in India. Of considerable interest is the adoption of Ayurveda by the mainstream medical system in some European countries (e.g., Hungary), emphasizing this modality is increasing worldwide recognition. From ancient times, some of these herbal preparations have been used in the treatment of diabetes. This paper reviews the accumulated literature for 10 Indian herbs that have antidiabetic activity and that have been scientifically tested. Few of these herbs, such as *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum greacum*, have been reported to be beneficial for treating type 2 diabetes. Mechanisms such as the stimulating or regenerating effect on beta cells or extrapancreatic effects are proposed for the hypoglycemic action of these herbs.

INTRODUCTION

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by an absolute or relative deficiency of insulin and insulin resistance. Lack of insulin, whether absolute or relative, affects the metabolism of carbohydrates, proteins, fats, water, and electrolytes. World Health Organization (WHO) recommendations (WHO, 1980) on the use of alternative medicines for treating diabetes mellitus provide an impetus for research in this area. Currently, the focus of research in diabetes includes discovering newer antidiabetic agents as well as isolating the active compounds from herbal sources that have been documented to have antidiabetic properties as have been described in ancient texts (Tripathi, 1998).

Alternative systems of medicine, such as Ayurveda and Unani, have been used widely in India. Ayurveda encompasses knowledge of life, known and unknown and is used to cure disease and preserve health (Pendse and Iyengar, 1961).

In Ayurveda diabetes falls under the term *Madhumeha*. Various types of herbal preparations such as decoctions

(boiled extracts), *Swaras* (expressed juices), *Asav-Arisht* (fermented juices), and powders have been mentioned for the treatment of *Madhumeha*. (Tripathi, 1998). These formulations are basically of plant origin but some inorganic compounds and animal products have also been used (Sharma, 1993). These indigenous medicines may not have adverse effects in therapeutic doses. It is mentioned in ancient texts such as the *Charak Samhita* (Shastri, 1994) that a single herb exerts different actions on many diseases and that each herb may have one dominating effect and other comparatively subsidiary effects. It is also mentioned that an herbal drug can also have synergistic and antagonist effects in combination with other herbs (Pendse and Iyengar, 1961).

More than 800 plants are used as traditional remedies in some form or another for the treatment of diabetes according to ethnobotanical information (Ajgaonkar, 1979; Alarcón-Aguilara et al., 1998). However, only a few herbs have been evaluated scientifically. This review focuses on the role of animal or clinical studies on 10 herbs that are mentioned in Ayurveda for the treatment of diabetes.

BITTER MELON

Bitter melon (*Momordica charantia*) in the Cucurbitaceae family is a slender-stemmed tendril climber, cultivated in tropical areas including India, Asia, and South America. *Swaras* of fruit has been used as a hypoglycemic agent in Ayurveda (Sharma, 1996).

Scientific evidence and proposed mechanism of action

M. charantia fruit has been evaluated in many animal studies; however, relatively few reports are available on its activity in humans.

Significant reduction of blood glucose level and increased concentration of plasma insulin has been observed in rats with diabetes who were treated with fruit juice of *M. charantia*. This is probably the result of an increase in the number of beta cells in treated animals compared to untreated ones (Ahmed et al., 1999a). Recently Vikrant et al. (2001) investigated the effect of *M. charantia* along with *Eugenia jambolana* on insulin resistance in fructose-fed diabetic rats. The water extract of these plants in a dose of 400 mg/d reduced hyperglycemia and also reduced insulin levels.

A hypolipidemic effect was observed when fruit juice was administered to rats with streptozotocin-induced diabetes for 10 weeks. It decreased plasma cholesterol and triglycerides and increased high-density lipoprotein (HDL) levels in the animals (Ahmed et al., 2001). The juice also delayed the nonretinal ocular diseases of diabetic rats. Lenticular opacity appeared earlier in untreated rats compared to those treated with fruit juice of *M. charantia* (Srivastava et al., 1987). Another study reported that daily administration of fruit extract delayed the development of cataract in diabetic rats (Srivastava et al., 1988).

Grover et al. (2001) elucidated the effect of this plant along with other herbs (such as *Eugenia jambolana*, *Tinospora cordifolia*, and *Mucuna pruriens*) on diabetic nephropathy in rats and observed that the herb reduces polyuria ($p < 0.001$), partially prevents renal hypertrophy, and reduces urinary albumin excretion compared to untreated diabetic control rats.

A clinical study comprising 100 patients with type 2 diabetes, conducted for 2 days, showed that, on the first day the patients' pretreatment mean fasting blood glucose was 152 mg% and after an oral glucose tolerance test (OGTT), their mean 2-hour postprandial glucose level was 257 mg%. On the second day, an *M. charantia* extract was given 1 hour prior to blood testing. The patients' mean fasting glucose level was 131 mg%, which was significantly different from that of the previous day ($p < 0.001$). Similarly, after 75 g OGTT was taken, OGTT, patients' mean 2-hour blood glucose was reduced to 222 mg% in 86 patients. Although this study was conducted with a larger sample size the study ran

for a short duration (Ahmad et al., 1999b). Another study in which the fruit juice was administered before the OGTT to 18 patients with type 2 diabetes, a significant improvement in glucose tolerance was observed in 13 patients, while 5 patients experienced no significant improvement (Welihinda et al., 1986b).

The phytochemical momordicin, charantin, and a few compounds such as galactose-binding lectin (Ng et al., 1986b) and insulin-like protein (plant insulin) (Ng et al., 1986a) isolated from various parts of this plant have been shown to have insulin mimetic activity. Recently Murthy et al. (2002) purified three compounds called kakara-1b, -111a and -111b from this plant and showed their hypoglycemic effect in mildly diabetic rabbits at doses of 400, 100, and 300 mg/kg per day.

The mechanisms proposed for the hypoglycemic effect of *M. charantia* have been attributed to an inhibitory effect on glucose absorption in the intestine (Meir and Yaniv, 1985), enhanced insulin release from beta cells (Higashino et al., 1992), and an extrapancreatic effect via increased glucose uptake by tissues *in vitro* (Welihinda et al., 1986a). Fruit juice of this plant was also observed to increase the number of beta cells in treated diabetic animals compared to untreated animals ($p < 0.004$; Ahmed et al., 1998).

It was observed that insulin reverses the changes in expression and activity of cytochrome P-450 (CYP-450) isoenzymes in hepatic and renal microsomes of spontaneous or chemically induced diabetic rats (Dong et al., 1988; Favreau et al., 1988). The fruit juice of *M. charantia* was observed to reverse the activities of some hepatic CYP-450 isoenzymes and also increase the activity of glutathione (GSH) in the liver of diabetic rats. The herb also exerted varied effects on CYP-450 isoenzyme expressions in the livers of diabetic and control rats (Raza et al., 1996).

Raza et al. (2000) reported further that the fruit juice of this plant reversed the effect of chronic diabetes on modulation of CYP450-dependent monooxygenase activities, GSH-dependent, oxidative-stress-related lipid peroxidation and glutathione-S-transferase (GST) activities. These researchers noted that *M. charantia* normalized the alteration in some drug-metabolizing enzymes in patients with diabetes and that this may be the result of the presence of multiple agents in the fruit juice.

FENUGREEK

Fenugreek (*Trigonella foenum-graecum*) in the Leguminosae family is an annual herb, native to western Asia and southeastern Europe, that is cultivated worldwide (e.g., the Mediterranean region, China, and northern India) (Kirtikar and Basu, 2000).

*GSH, reduced form of glutathione.

Scientific evidence and proposed mechanism of action

Several experimental and few human studies have demonstrated the hypoglycemic effect of *T. foenum-graecum* seeds.

Ajbnor et al. (1988) observed the hypoglycemic effect of a decoction and an ethanol extract of *T. foenum-graecum* seed on the serum glucose levels of normal and alloxan-induced diabetic mice. A significant reduction was observed in the mice's fasting blood glucose as a result of administering the decoction and the ethanol extract. This effect was comparable to that observed with tolbutamide. In another study, a significant reduction was observed in diabetic rats' fasting blood glucose by approximately 300 mg% after administering the seed powder for 21 days (Raju et al., 2001). Vats et al. (2002) studied the hypoglycemic effect of *T. foenum-graecum* along with other herbs and observed a significant reduction in fasting blood glucose level by approximately 15 mg% in normal and in diabetic rats by approximately 80 mg% ($p < 0.001$).

In a double-blinded placebo-controlled trial, Gupta et al. (2001) showed that seeds of *T. foenum-graecum* reduced insulin resistance by decreasing insulin levels approximately 7% and increasing insulin sensitivity approximately 56%. The seeds also decreased serum triglyceride levels by approximately 53mg% with no effect on total cholesterol and low-density lipoprotein (LDL) levels. A major drawback of this study was that the sample size was too small to arrive at definite conclusions. These observations must be tested with a larger sample size to derive valid conclusions.

Sharma et al. (1990) studied the antidiabetic properties of *T. foenum-graecum* seeds in 10 patients with type 1 diabetes. Patients were put on a fixed dose of insulin throughout the study and randomly assigned to an isocaloric diet, with or without *T. foenum-graecum* defatted seed powder twice per day in chapatti. The patients' mean fasting blood glucose was reduced significantly from baseline by approximately 76 mg% ($p < 0.01$). Statistically significant decreases of serum total cholesterol, triglycerides, and LDL was also reported.

T. foenum-graecum contains an alkaloid trigonelline (Bever, 1980; Nadkarni, 1954), which has been shown to have hypoglycemic action. However, opinion varies regarding the active compounds and their mechanisms of action. Ali et al. (1995) isolated a soluble dietary fiber, galactomannan, from *T. foenum-graecum* seeds, which is involved in lowering the postprandial glucose level in type 2 diabetic rats. An amino acid 4-hydroxyisoleucine extracted from the seeds of *T. foenum-graecum* has been observed to cause glucose-induced insulin release *in vitro* (Sauvaire et al., 1998) and *in vivo* (Broca et al., 1999). *In vivo*, 4-hydroxyisoleucine has been shown to improve glucose tolerance in normal rats and dogs. After administration for 6 days, 4-hydroxyisoleucine reduced basal hyperglycemia, decreased basal in-

sulin levels, and also improved glucose tolerance significantly in type 2 diabetic rats. Recently, furostanol saponins called trigoneosides glycoside D and trigofaenoside A (Yoshikawa et al., 1997), and steroidal sapogenins such as diosgenin and yamogenin (Taylor et al., 2000) were isolated from this plant. *T. foenum-graecum* may lower glucose levels by improving peripheral glucose utilization (Raghuram et al., 1994). The plant also delays gastric emptying and reduces the absorption of glucose from the small intestine, thus suggesting pancreatic as well as extrapancreatic effects (Anderson et al., 1979).

T. foenum-graecum modulates many biochemical events associated with glucose metabolism as shown in experimentally induced diabetes. Raju et al. (2001) showed that *T. foenum-graecum* seeds decrease fasting blood glucose probably by reversing the activities of gluconeogenic, glycolytic, and lipogenic enzymes in the livers and kidneys of diabetic rats. Activities of glycolytic enzymes (phosphofructokinase, pyruvate kinase, and lactate dehydrogenase) were lower in liver and higher in the kidneys of diabetic rats; however, the activities of NADPH[†]-linked lipolytic enzymes were lower in both tissues. *T. foenum-graecum* seeds reversed the activities of these enzymes to a level of controls and also decreased the activities of gluconeogenic enzymes (glucose-6-phosphatase, fructose-1,6-biphosphatase) in the livers and kidneys of rats. Raju et al. (1999) reported that sodium orthovanadate and *T. foenum-graecum* seed powder partially restored the activity of glyoxalase I enzyme compared to controls, which is decreased in livers and cytosol of diabetic rats. Another study showed that this combination restored the mRNA levels of two key enzymes of gluconeogenesis (glucose-6-phosphatase, fructose-1,6-biphosphatase) to normal, which are increased in liver and kidney of diabetic rats (Baquer et al., 2002).

Genet et al. (1999) reported that there was a significant improvement in the activity of creatine kinase caused by sodium orthovanadate and *T. foenum-graecum* seed powder. This reversal was effective in tissues such as muscles and livers, which are insulin-dependent for the metabolism of glucose. The researchers hypothesized that this might be the result of the insulin-mimetic effect of sodium orthovanadate and explained further that this combination restored the energy level to control levels by inhibiting adenosine triphosphatase (ATPase) thereby increasing the levels of adenosine triphosphate (ATP) and controlling phosphorylation and dephosphorylation of regulatory cytosolic and mitochondrial enzymes involved in utilization and generation of ATP. *T. foenum-graecum* also reduced lipid peroxidation and increased levels of GSH and β -carotene, showing a potential to reduce complications of diabetes (Ravikumar et al., 1999).

[†]NADPH, reduced form of nicotinamide adenine dinucleotide phosphate.

INDIAN KINO TREE

The Indian kino tree (*Pterocarpus marsupium*) in the Leguminaceae family is a large deciduous tree, native to southern India, is distributed in the country's west peninsula and in Sri Lanka. A water extract of the wood of this plant has been used for treating diabetes mellitus since ancient time (Sharma, 1996).

Scientific evidence and proposed mechanism of action

A number of experimental and clinical studies in animals have documented the hypoglycemic activity of this plant. In one study, the ethyl acetate-soluble fraction of an ethanol extract of the wood of this plant was administered to rats for 5 days after alloxan administration. A significant reduction was observed in fasting blood glucose by 70% compared to control rats. Improved glucose tolerance along with increased levels of the pancreatic insulin and proinsulin biosynthesis in islets of rats was also observed (Ahmad et al., 1991a). A significantly hypoglycemic effect was observed in normal rats (approximately 11 mg%), 2 hours after oral administration of the aqueous extract of this plant. It also lowered the blood glucose in rats with significantly alloxan-induced diabetes (by approximately 117mg%), 21 days after daily administration of the extract (Vats et al., 2002).

In a clinical study, 10 patients were given water stored in a heartwood container of this plant for a period of 1 month. Blood glucose levels decreased from the second week of treatment and were maintained at a normal level until the treatment was withdrawn (Keder and Chakrabarti, 1981). Another flexible-dose open trial evaluated the efficacy of this plant for treating newly diagnosed or untreated patients with type 2 diabetes. A plant extract was given to patients for total period of 12 weeks. Initially, 2 g of herb extract was given to the patients for 4 weeks. The dose was increased up to 4 g if no significant effect was observed. Among 93 patients who completed the study, both fasting and postprandial blood glucose levels decreased significantly ($p < 0.001$) by 32 mg% and 45 mg% 12 weeks after the initial mean values of 151 mg% and 216 mg%, respectively (Indian Council of Medical Research [ICMR], 1998).

An active principle (–) epicatechin isolated from the bark of *P. marsupium* has been found to have protective and restorative effects on beta cells in diabetic subjects. Possibly, (–)epicatechin acts by regenerating the beta cells and may produce actions similar to the effects of insulin (Ahmad et al., 1989; Chakraverty et al., 1981).

Ahmed et al. (1991(b)) observed that (–)epicatechin increases the cyclic adenosine monophosphate (cAMP) content in pancreatic islets, which in turn, are associated with the increase in insulin release, conversion of proinsulin to insulin, and cathepsin-B activity in mature (12 months old) and immature (1 month old) rats pancreatic islets *in vitro*.

The effect was more pronounced in immature rats. In another *in vitro* study (–)epicatechin was observed to elicit a protective effect on the osmotic fragility of human erythrocytes similar to the effect of insulin (Rizvi et al., 1995).

GYMNEMA

Gymnema (*Gymnema sylvestre*), also known as periploca of woods in the Asclepediaceae family is a large woody highly branched climber, native to southern India, that is distributed in Sri Lanka and tropical Africa. Leaves of *G. sylvestre* in the form of powder are used as an antidiabetic agent (Sharma, 1996).

Scientific evidence and proposed mechanism of action

Many experimental and clinical studies have documented the hypoglycemic action of this plant. In an animal study, it was observed that an aqueous extract (GS4) of this plant improved glucose tolerance when administered in rats with experimentally induced diabetes (Okbayashi et al., 1990).

One clinical study demonstrated the effectiveness of a GS4 extract, when administered as a supplement to conventional oral hypoglycemic agents to 22 patients with type 2 diabetes for a period of 18–20 months versus 25 patients who were receiving conventional oral hypoglycemic agents for same periods. A statistically significant reduction was observed in the patients' mean fasting blood glucose level by ~50 mg% after 18 months and the mean glycosylated hemoglobin A_{1c} (HbA_{1c}) decreased from a baseline of 11.9% to 8.34% ($p < 0.001$) in the subjects who received the GS4 extract. The dosage of conventional oral hypoglycemic agents had to be reduced to prevent hypoglycemia. Five (5) of 22 patients were able to discontinue their conventional oral hypoglycemic agents and blood-glucose homeostasis was maintained by GS4 extract alone. Significant reduction in plasma lipid levels was also observed, suggesting hypolipidemic effect of this plant (Baskaran et al., 1990).

In another study of patients with type 1 diabetes, GS4 extract was administered to 27 patients along with insulin for the periods ranging from 2–30 months, compared to 37 controls receiving insulin only. It was observed that insulin dosage had to be reduced by approximately 25% after 6–8 months and by approximately 50% after 26–30 months, respectively, while mean fasting blood glucose level reduced considerably. Reductions in serum amylase, lipids and HbA_{1c} levels were also observed by GS4 extract. Serum C-peptide levels were also increased after supplementation of leaf extract, suggesting an increase in beta cell function (Shanmugasundaram et al., 1990b).

Water-soluble extracts (GS3 and GS4) obtained from leaves release insulin probably by causing regeneration of pancreatic beta cells both *in vivo* and *in vitro* (Shanmuga-

sundaram et al., 1990a). *In vitro* studies reported that the GS4 extract stimulates insulin release from beta cell lines and from pancreatic islets in the absence of any other stimuli, suggesting that it releases insulin by increasing beta cell permeability rather than stimulated exocytosis by regulating pathways (Persaud et al., 1999). *G. sylvestre* also increases the activities of the enzymes involved in glucose utilization by insulin-dependent pathways thereby correcting the metabolic derangements in liver, kidney, and muscles of diabetic rabbits (Shanmugasundaram et al., 1983).

TUMERIC

Tumeric (*Curcuma longa*), a member of the Zingiberaceae family, is a perennial herb, native to southern Asia, extensively cultivated in India, China, and other tropical countries. Traditionally rhizome of *C. longa* has been used in form of expressed Juice along with fruit of *Embilica officinale* (*Awala*), for treating diabetes (Sharma, 1996).

Scientific evidence and proposed mechanism of action

In Ayurveda, *C. longa* is advocated extensively for the treatment of diabetes but few scientific studies are available in the modern literature. Curcumin, an active ingredient isolated from *C. longa*, has been shown to have hypoglycemic, hypolipidemic, and antioxidants effect in experimental studies.

Recently, it was reported that curcumin decreases blood glucose, HbA_{1c} in diabetic rats. In addition, curcumin also decreased oxidative stress in diabetic rats. It was found that the levels of thiobarbituric acid reactive substance (TBRAS) decrease after supplementation of curcumin. They hypothesized that it may be the result of decreased influx of glucose in polyol pathway, thereby increasing NADPH/NADP ratio and increased activity of glucose peroxidase enzyme (Arun and Nalini, 2002).

The beneficial effect of curcumin has been suggested in diabetic dyslipidemia, without altering the hyperglycemic status in diabetic rats. Babu et al. (1997) observed a significant reduction in blood cholesterol in curcumin fed diabetic rats and this reduction was exclusively from LDL very low density lipoprotein (VLDL) fraction. A significant reduction in serum triglycerides and phospholipids were also observed. Curcumin also increase the activity of β -hydroxy- β -methylglutaryl-coenzyme A (HMG-CoA) reductase and hepatic cholesterol-7 α -hydroxylase enzymes in diabetic rat livers.

It was reported that hypercholesterolemia may possess an additive risk factor that determines the rate of decline in kidney function in diabetes. They observed that patients with diabetic nephropathy and high serum cholesterol levels exhibit higher degrees of renal lesion (Mulec et al., 1990). Excretion of larger amounts of proteins of higher molecular weight and renal tubular enzymes is associated with diabetic

nephropathy. It was observed that the diabetic animals fed on curcumin diet reduced excretion of these proteins and urinary enzymes than control diet fed rats significantly (Suresh Babu and Srinivasan, 1998). Same group of investigators (Suresh Baba and Srinivasan, 1995) have been reported previously that curcumin-fed diabetic rats excreted comparatively lower amounts of albumin, urea, creatinine, and inorganic phosphorus. These observations led to the hypothesis that curcumin ameliorates the early renal lesions associated with diabetes, as a result of its cholesterol-lowering ability without altering hyperglycemic status (Suresh Babu and Srinivasan, 1998).

Curcumin also has an antioxidant property. It not only inhibits lipid peroxidation significantly in rat liver microsomes, but also reduces the increased accumulation of advanced glycation end products (AGEs) and cross-linking of collagen in tail tendon and skin of diabetic animals, thereby preventing AGEs induced complications of diabetes (Reddy et al., 1992; Sajithlal et al., 1998). Curcumin enhanced wound repair in diabetic animals and could be developed as pharmacologic agent in diabetic ulcers (Sidhu et al., 1999).

TINOSPORA

Tinospora, (*Tinospora cordifolia*) is a member of the Menispermaceae family is large glabrous climber, indigenous to India and is also found in Myanmar and Sri Lanka. Traditionally, stem and root plant parts have been used in form of decoction and *swaras*, in diabetic patients (Sharma, 1996).

Scientific evidence and proposed mechanism of action

The use of *T. cordifolia* in a few animal studies has shown hypoglycemic, hypolipidemic, and antioxidant effect. The possible mechanism by which root of this plant brings about its hypoglycemic action may be by increasing the secretion of insulin from beta cells. It may also have action on activity of hexokinase and may decrease the activity of hepatic glucose-6-phosphatase in diabetic rats (Stanely et al., 2000).

Gupta et al. (1967) showed that aqueous and alcoholic extract of this plant increases glucose tolerance in albino rats. In another study a significant reduction was observed in mean fasting blood glucose by approximately 128 mg% and by approximately 130 mg% after supplementation of 2.5 g/kg and 5.0 g/kg dose of root extract, respectively to alloxan induced diabetic rats. (Stanely et al., 2000). The antioxidant activity of this plant was also evaluated in diabetic rats reported by Prince et al. (1999). Plasma concentration of TBRAS, ceruloplasmin, and alpha-tocopherol increases in diabetic rats due to increased lipid peroxides. These researchers reported that root extract of this plant decreases the elevated levels of ceruloplasmin, alpha-tocopherol, and TBRAS in diabetic rats. On the other hand it also increases

the plasma concentration of vitamin-C and GSH (Prince et al., 1999) which act as inhibitors of free-radical-mediated lipid peroxidation (Meistor and Anderson, 1983).

MARGOSA TREE

The Margosa tree, (*Azadirachta indica*) a member of the Meliaceae family, is indigenous to India, Sri Lanka, and also found in other tropical regions including Indonesia and Australia. Seed oil, expressed juice of leaves, and the bark of this plant, along with other herbs have been used as a hypoglycemic agents since ancient times (Kirtikar and Basu, 2000).

Scientific evidence and proposed mechanism of action

The hypoglycemic effect may be the result of action on extrapancreatic sites (i.e., by increased peripheral glucose utilization by blocking the action of epinephrine on glucose metabolism; Chattopadhyay, 1996). Increased glucose uptake and glycogen deposition in isolated rat hemidiaphragm has also been observed (Chattopadhyay et al., 1987). One experimental study has documented the hypoglycemic action of leaf extract and seed oil in normal and alloxan diabetic rabbits. After administering leaf extract for 4 weeks, the blood glucose levels decreased significantly by approximately 136 mg%, and in the case of seed oil administration, the decrease in blood glucose was approximately 123 mg% in diabetic rabbits ($p < 0.001$) compared to controls. The effect of this plant was comparable to glibenclamide given as standard drug for comparison to a group of rabbits (Khosla et al., 2000).

IVY GUARD

Ivy guard (*Coccinia indica*), a member of the Cucurbitaceae family, is perennial tree, native to India and distributed to Sri Lanka, Malaysia, and tropical Africa. The leaves and thick taproot of this plant has been used since ancient times by Ayurvedic physicians as an adjunct to metallic preparations in treatment of diabetes (Sharma, 1996).

Scientific evidence and proposed mechanism of action

C. indica demonstrates a hypoglycemic effect documented by few scientific studies. Shibib et al. (1993) used *C. indica* leaves in a dose of 200 mg/kg and observed a decrease in blood glucose level by approximately 23 mg% and approximately 27 mg% in normal and streptozotocin induced diabetic rats, respectively. The authors ascribed this effect to suppression of hepatic glucose-6-phosphatase and fructose-1,6-biphosphatase enzymes.

A clinical study suggested that an ingredient present in extract of *C. indica* acts similar to insulin by reducing the

activity of glucose-6-phosphatase and lactate dehydrogenase (LDH) in glycolytic pathways and reversed significantly the depletion of lipoprotein lipase (LPL) activity in lipolytic pathways. Mild diabetes had no effect on LPL, LDH, and glucose-6-phosphatase compared to normal but changes in activities of these enzymes were found with increased severity of disease (Kamble et al., 1998).

In a double-blinded controlled trial, the leaves of *C. indica* also improved glucose tolerance in patients with uncontrolled type 2 diabetes. Ten (10) out of 16 patients in the treated group showed significant improvement in blood glucose level (Azad Khan et al., 1979).

HOLY FRUIT TREE

Holy fruit tree (*Aegle marmelose*), a member of the Rutaceae family, is a perennial tree of 7.62–9.14 m height that is native to India but also grows in several areas of southeast Asia. Leaf extract in form of expressed juice and fruit of *A. marmelose* has been used since ancient times (Sharma, 1996).

Scientific evidence and proposed mechanism of action

The leaf extract of *A. marmelose* has been shown to have a hypoglycemic activity similar to that of insulin when given orally to rats with alloxan-induced diabetes. It decreased blood glucose levels near to controls and increased the glucose tolerance. On the other hand, leaf extract also decreased serum cholesterol by approximately 93 mg% and brought back body weight to control levels, which were decreased in diabetic rats (Ponnachan et al., 1993).

The mechanism of hypoglycemic action is not clear but may be the result of improvement in the functional status of beta cells, and by reversing the histologic and ultrastructural changes in the pancreas and livers of rats with streptozotocin-induced diabetes (Das et al., 1996). The leaf extract of this plant also exhibits the effect on metabolic enzymes involved in glucose metabolism. The kinetic parameters such as Michelle's constant (K_m) and V_{max} value of liver enzyme malate dehydrogenase (MDH) and its purified cystolic isoenzyme (S-MDH) were increased significantly in the diabetic state compared to respective controls. Insulin as well as leaf extract treatment brought about a reversal of K_m values to near normal but did not reverse the V_{max} value of the enzymes. Because MDH is an important enzyme in glucose metabolism, the variation in its quantitative and qualitative nature may contribute to pathological status of diabetes (Seema et al., 1996).

POMEGRANATE

Pomegranate (*Punica granatum*), a member of the Punicaceae family is a shrub or small tree, probably originated

in Asia, and is widespread in the Mediterranean region as far as the southern Tyrol, near east Africa, South Africa, and China. The seeds of *P. granatum* have been used for the treatment of diabetes in various formulations indicated in Ayurveda literature. The flowering part of this plant has also been recommended as treatment of diabetes in Unani literature (Kirtikar and Basu, 2000).

Scientific evidence and proposed mechanism of action

Various parts of this plant such as the rind, flower, and seeds exhibit antidiabetic effects. Recently, the hypoglycemic activity of seeds was reported in rats with experimentally induced diabetes. In this study the methanol extract of seeds in doses of 300 mg/kg and 600 mg/kg were supplemented orally to diabetic rats, resulting in significant reduction of blood glucose level by 47 mg% and 52 mg%, respectively, at the end of 12 hours (Das et al., 2001). In another study, various doses of flower extract were administered to normal rats, glucose-fed rats, and rats with streptozotocin-induced diabetes. All doses of extract were found to be effective in decreasing blood glucose level, but the maximum effect was observed for a dose of 400 mg/kg (Jafri et al. 2000).

The mechanism of hypoglycemic action is not clear. A variety of hypothesized mechanisms include increased peripheral glucose utilization (Jafri et al., 2000) and inhibition of proximal tubular reabsorption mechanism for glucose in kidney (Sharma et al., 1983).

DISCUSSION

Advances have been made in the understanding of the hypoglycemic action of various herbs but many questions remain unanswered. As mentioned earlier, most of the plants exhibited hypoglycemic, hypolipidemic, and antioxidant effects in animals as well as in humans, which may be helpful in diabetes and associated complications. The exact mechanism of action of these plants still needs to be elucidated. On critical analysis of the available studies, it is observed that most of the plants stimulate beta cells to release insulin. Few plants such as *G. sylvestre*, *M. charantia*, *P. marsupium*, et cetera may also help in regeneration or increase in the number of beta cells, which is an important discovery because none of the conventional oral hypoglycemic agents exhibit this action (Ahemad et al., 1998; Chakravarthy et al., 1981; Shanmugasundaram et al., 1990a).

Plants such as *P. granatum* and *A. indica* also exhibit extrapancreatic effects via peripheral glucose utilization (Chattopadhyay, 1996; Sharma et al., 1983). Increased glucose uptake by tissues *in vitro* (Welihinda et al., 1986a) and decrease in gastric emptying (Anderson et al., 1978) has also been demonstrated by herbs such as *M. chirantia* and *T. foenum-graecum*. An amino acid 4-hydroxyisoleucine ex-

tracted from the *T. foenum-graecum* seed is a novel potentiator of insulin secretion and is very specific on beta cells (Broca et al., 1999). The insulinotropic activity of this amino acid is directly dependent on the concentration of glucose in hyperglycemic condition. Presence of various active ingredients in these herbs, with actions either similar to insulin or increase insulinotropic action needs to be further researched.

Recent reports (Raju et al., 2001; Shibib et al., 1993; Stanely et al., 2000) describe the role of few herbs (e.g., *T. foenum-graecum*, *T. cordifolia*, *C. indica*, *M. charantia*) on activities of enzymes involved in carbohydrate and lipid metabolism. Glucose-6-phosphatase catalyses terminal steps of gluconeogenesis and glycogenolysis. Fructose, 1-6 biphosphatase catalyses the irreversible step of gluconeogenesis and serves as a site for regulation of the process. The above-mentioned herbs regulate the activities of these enzymes, thereby helping in better metabolic control of diabetes. Likewise, another herb *A. marmelose* controls the Km value of MDH enzyme, which is highly active in gluconeogenesis in diabetes (Seema et al., 1996). *T. foenum-graecum* has also shown to have an effect on the activity of glyoxalase 1 enzyme and creatinine kinase enzyme, by which it may be helpful in conduction of energy in diabetes (Genet et al., 1999; Raju et al., 1999).

An important active ingredient isolated from *P. marsupium* has been shown to have an effect on the activity of cathepsin-B and increases cAMP count in islets (Ahmad et al., 1991b). Cathepsin-B is responsible for conversion of proinsulin to insulin, which is an important effect showed by this herb. The activity of C-peptide is also increased by *G. sylevestre in vitro* (Shanmugasundaram et al., 1990b). On the other hand, the antioxidant action of these herbs (e.g., *M. charantia*, *C. longa*, *T. cordifolia*) may also be helpful in reducing the chronic complications of diabetes. *C. longa* reduces the lipid peroxidation (Reddy et al., 1992), and may be able to reduce diabetic dyslipidemia (Babu et al., 1997) and nephropathy in animals (Suresh et al., 1998). *M. charantia* has been shown to have delayed effect on nonretinal ocular disease (Srivastava et al., 1987) and nephropathy in diabetic rats (Grover et al., 2001) Therefore, only few herbs (e.g., *M. charantia*, *C. longa*, etc.) have been investigated for reducing complications.

These observations are based on few studies, most of which are animal studies of short duration and small sample size, which makes it inappropriate to comment on the efficacy of these herbs in humans. However, these observations need to be further evaluated in human beings. If proven to be effective, these herbs can be incorporated in the treatment of diabetes as alternatives to conventional hypoglycemic agents, thereby overcoming the limitations of conventional oral hypoglycemic agents such as undesirable side effects and tolerance.

These herbs can be better than other available oral hypoglycemic agents, because there are no uniform known toxic effects of these in therapeutic dosage, while they are traditionally being used since ancient times. However, fur-

ther research is needed to evaluate the toxicity or adverse effects, if any, of these herbs. It would also be useful to investigate the efficacy of single herb therapies versus the relative combination of herbs used. It is not clear from the currently available literature if the use of combination of herbs provide any additional benefit over the use of a single herb.

Therefore, available data on antidiabetic response of these herbs suggests that there are many active ingredients present in different parts of these herbs, which in turn act through different pathways and have role in many diseases apart from diabetes (Sharma, 1996).

CONCLUSION

In conclusion, only a few herbs have attracted the interest of scientists and have been put forward for investigations. These herbs reduce blood glucose as well as have beneficial effects on complications of diabetes. However, the pharmacologic actions of these compounds need to be evaluated in studies involving humans to justify the use of these plants or their active principles for the treatment of diabetes. Therefore, there is a need of more well-documented clinical trials and more laboratory work to isolate the active principles, their pharmacological actions and toxicity. An oral hypoglycemic agent having hypolipidemic, and antioxidant action would be better for the treatment of diabetes. Few of the herbs mentioned above may have all these actions and prove to be promising in the treatment of diabetes and its complications in the near future.

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