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Promising Antidiabetic Agents Of Natural Origin: An Overview



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ABSTRACT

Hypoglycaemic activity of chemical constituents isolated from antidiabetic medicinal plants, which are in traditional use against Diabetes mellitus, is reviewed up to 2004. It is anticipated that the present overview would boost up the challengers engaged in search of alternative effective drugs against the most alarming disease world-wide. © 2005 Trade Science Inc. - INDIA

BACKGROUND

Diabetes mellitus is the most prevalent metabolic syndrome world-wide with an incidence varying between 1 to 8%^[1,2]. The disease arises when insufficient insulin is produced, or when the available insulin does not function correctly. Thus diabetes is characterized by hyperglycaemia (elevation in blood sugar levels) resulting in various short-term metabolic changes in lipid and protein metabolism and long-term irreversible vascular changes. These include diabetes-specific complications of the micro-vasculature system (e.g. retinopathy, nephropathy and neuropathy) and complications of macro-vasculature system (eg. arteriosclerosis leading to heart diseases, stroke and peripheral vascular diseases) these com-

plications are also found in non-diabetic population, but have a two to five-fold increase in diabetic subjects^[3]. The last century has seen a rapid increase in the global prevalence of coronary artery disease (CAD)^[4,5]. Current estimates from different countries in Europe and the United States have shown that diabetes and its complications account for 8-16% of the total health costs for society and this will increase dramatically unless major efforts are made to prevent the ongoing epidemic. There are two major categories of diabetes-insulin dependent diabetes mellitus (IDDM) 1 and non-insulin dependent diabetes mellitus (NIDDM). IDDM diabetes occurs due to almost 95% destructions of beta cells of islets of Langerhans in the endocrine pancreas; this type has an early onset, most often between the ages 10 and

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16. NIDDM diabetes, on the contrary, is developed due to a loss of sensitivity to insulin of the cells of the body although insulin level is normal or more than normal; this type is the commonest form of diabetes constituting above 90% of the diabetic population. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025^[6]. The World Health Organization (WHO) has predicted that the major burden will occur in the developing countries; there will be a 42% increase from 51 to 72 million in the developed countries while 170% increase from 84 to 228 million, in the developing countries^[7]. Prevalence of the complications is greater among the lower socio-economic peoples due to lack of good control of glycaemia and hypertension and also due to behavioural factors. The direct and indirect costs involved in the treatment of the chronic disease especially when associated with the vascular complications are enormous. The overall global scenario urges to implement cost-effective and at the same time efficacious preventive measures against diabetes to reduce the high morbidity and mortality.

Back to the plant kingdom

The use of ethnobotanicals has long folkloric history for the treatment of blood sugar abnormalities. In the India, indigenous remedies have been used in the treatment of diabetes since the time of Charaka and Sushruta (6th century B.C)^[8]. Plants has always been exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The ethnobotanical information reports about 800 plants that may possess antidiabetic potential^[9]. Many of such plants have exhibited antidiabetic activity when assessed using presently available experimental techniques^[10-14]. It may be mentioned in this connection that the discovery of widely used hypoglycaemic drug, metformin came from the traditional approach of using *Galega officinalis*. In spite of all these, the indigenous system has not yet gained enough momentum in the scientific community. The reasons may be many including lack of belief among the practitioners of conventional medicine over alternative medicine, alternative form of medicine are not very well-

defined and natural drug may vary tremendously in content, quality and safety. Although, a few synthetic oral hypoglycaemia agents [e.g the glitazones (troglitazone, rosiglitazone, pioglitazone)-thiazolidinediones class of compounds; biguanides and sulfonylureas] and also insulin therapy are in use to ameliorate the sufferings to some extent, still no positive answer has yet been obtained^[15]. To cope with this severe problem there is a need to look for more efficacious drugs with lesser side effects and also of low cost. It is the high time to turn our attention to the plant kingdom in search of natural drugs for diabetes following an integrated approach and using correct procedures; if even a single plant material stands the acid-test of efficacy comparable to commonly used synthetic oral drugs already marketed, it will herald the discovery of cheap and relatively non-toxic drug.

A number of review articles^[16-19] on the uses of various plants (different parts of plant materials, crude extracts, etc.) as antidiabetic agents have been published time to time; thus the purpose of this present review is to focus on the studies of antidiabetic efficacy of only the chemical constituents derived from the so called plant materials, which may tempt the scientific community, especially those who are working in this field, to develop new drug for the future.

Studies on antidiabetic efficacy of chemical constituents of natural origin

Antidiabetic studies were carried out with a number of chemical constituents derived from plant materials, which have been used as traditional remedies against Diabetes mellitus. This section offers an overview of the results of the works studied so far.

Swerchirin (1,8-dihydroxy-3,5-dimethoxyxanthone), isolated from the hexane extract of *Swertia chirayita*, was found to have a significant antidiabetic activity in fasted, fed, glucose-loaded and tolbutamide-pretreated albino-rat models; the effective dose (ED₅₀ value) for lowering blood sugar by 40% in Charles Foster (CF) strain male albino rats (body weight 140-165 g) was determined to be 23.1 mg/kg (oral)^[20]. A similar study on the hypoglycaemic effect of Swerchirin in healthy as well as streptozotocin (STZ)-induced diabetic CF albino rats revealed a very

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significant drop in blood glucose level 7h after single drug administration (50 mg/kg, p.o., suspension in gum acacia fed through cannula) in both the groups^[21]. The work of Saxena et al^[22] offers an insight into the mechanism of blood sugar lowering by crude/impure Swerchirin, isolated from the hexane extract of *S. chirayita*, single oral administration of which (50 mg/kg, body weight) to fed CF rats resulted 60% fall in blood glucose by 7h post-treatment. This was found to be associated with marked depression of aldehyde-fuchsin stain beta-granules and immunostained insulin in the pancreatic islets. *In vitro* glucose uptake and glycogen synthesis by muscles (diaphragm) was significantly enhanced by the serum of Swerchirin-treated rat. It was observed that at 100, 10 and 1 µg final concentration, Swerchirin greatly enhanced glucose (16.7 mM)-stimulated insulin release from isolated islets. On the basis of these findings, the investigators suggested that Swerchirin lowers blood glucose level by stimulating insulin-release from islets of Langerhans.

The same group carried out a comparative study on the antidiabetic efficacy of two chemical compounds, tolbutamide (TB) and centpiperalone (CP) with Swerchirin-rich fraction (SW 1) of *Swertia chirayita* in experimental rat models. After a single oral administration of TB, CP and SW 1 to groups of normal and STZ-induced mild and severe diabetic rats, the blood sugar lowering effect (in terms of ED₅₀ values) was determined. Plasma immunoreactive insulin (IRI) levels and the degree of islet beta-cell degranulation were assayed using RIA and histochemical staining, respectively, in normal rats treated with the agents. The percent blood sugar lowering, increase in IRI level and beta-cell degranulation were highest in CP-treated normal rats (69, 124 and 75%, respectively). In addition, CP was the only agent found active in STZ-induced severely diabetic rats (P<0.01). In STZ-induced mild diabetic rats, however, TB was more effective than CP and SW 1. By analysis of data using Anova method, it is concluded that CP is more effective than SW 1 (P<0.01) and TB. However, SW1, an impure natural product showed better blood sugar lowering than tolbutamide which is a drug in use^[23].

Banset et al. studied the antidiabetic effect of

bellidifolin (1,5,8-trihydroxy-3-methoxyxanthone), another xanthonoid isolated from the ethylacetate fraction of *Swertia japonica*, and showed that the drug exhibits a potent and dose-dependent hypoglycaemic activity (26% decrease in blood glucose level) in normal as well as STZ-induced diabetic rats upon either oral or intraperitoneal administration at a dose of 50 mg/kg^[24]. Both bellidifolin and swerchirin showed significant activity, but bellidifolin was found more potent than swerchirin. The drug also significantly lowers the blood-triglyceride level; it was found to stimulate glucose uptake activity in Rat 1 fibroblasts expressing human insulin receptors. The workers assumed that the drug might work directly as a hypoglycaemic agent on peripheral tissues by means of a similar mechanism to that of vanadate, or it may have an activity similar to that of the extrapancreatic action of sulfonylurea^[25].

S-methyl cysteine sulfoxide and S-allyl cysteine sulfoxide from onion and garlic ameliorated the diabetic status of alloxan diabetic rats^[26]. S-methyl cysteine sulfoxide (from onion) exhibited anti-diabetic hyperlipidaemic activity in diabetic rats. The effects were comparable to those of glibenclamide and insulin^[27].

Triterpenoid saponins have been found to possess significant hypoglycaemic activity. The effect of gymnemic acid, a mixture of a number of triterpene saponins from the Indian medicinal plant *Gymnema sylvestre*^[28], on the elevation of blood glucose concentration induced with oral sucrose in STZ-diabetic rats was studied by Kang et al^[29]. Rats with STZ-induced diabetes mellitus and loaded orally with 4 g sucrose/kg were given one to four doses of 400 mg gymnemic acid/kg around the time of sucrose administration. It was observed that gymnemic acid has dose-dependent hypoglycaemic activity. In addition, *Gymnema* is reported to increase glucose uptake and utilization, and improve the function of pancreatic beta-cells. It may also decrease glucose absorption in the gastro-intestinal tract. Besides gymnemic acids (a mixture of triterpenoid saponins), other active principles of *Gymnema* are believed to be sterols (stigmasterol, quercitol), amino acid derivatives (betaine, trimethylamine, choline), and recently reported gymnemosides a and b. The saponin

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isolated from the leaves of *Acanthopanax senticosus* has been reported to decrease various cases of experimental hyperglycaemias (100, 200 mg/kg, i.p) induced by the injection of adrenalin, glucose and alloxan, without effecting the levels of blood sugar in normal mice^[30,31]. The hypoglycaemic effect of total saponins of *Aralia decaisneana* in rat and mice models was also investigated^[32]. The saponins decreased normal euglycaemic level to some extent, and decreased adrenaline-induced hyperglycaemia and alloxan-induced diabetic hyperglycaemia but not glucose-induced hyperglycaemia in mice.

Azadirachta indica (Indian neem) is used for the treatment of diabetes in Indian folklore. It has been observed that aqueous extract of neem leaves significantly decreased blood sugar level and prevents adrenaline as well as glucose-induced hyperglycaemia^[33]. Aqueous leaf extract also reduces hyperglycaemia in streptozotocin-induced diabetes and the effect is possibly due to presence of a flavonoid, quercetin^[34]. The leaf extract of *A.indica* has been reported to block the effects of epinephrine on glucose metabolism and reduction in peripheral glucose utilization in diabetic rats and to some extent in normal rats, indicative of hypoglycaemic potential of the plant^[35]. Khosla et al. and also Gosain et al. studied the hypoglycaemic effect of neem leaf extract and seed oil (containing nimbidin, a crude bitter principle), in normal as well as alloxan-induced diabetic rabbits^[36,37]. The effect, however, has been observed more pronounced in diabetic animals where administration for 4 weeks after alloxan-induced diabetes, significantly reduced blood glucose levels. Hypoglycaemic effect was found to be comparable to that of glibenclamide.

Trigonella foenum graecum (fenugreek) is commonly used as a spice in cooking and in small quantities is categorized as 'Generally Recognized as Safe' by the U.S. food and drug administration. Much of hyperglycaemic effect of fenugreek seeds in clinical studies is likely due to the inhibitory effects of mucilaginous fibres on glucose absorption. Clinical studies, in general, have shown a decrease in both fasting (up to 30%) and postprandial blood glucose levels (20-35%), HbA_{1C} (12%) and in some cases cholesterol and TG levels. Bioactive compounds isolated

from fenugreek seeds includes saponins (e.g. fenugreekine, diosgenin), alkaloids (e.g. trigonelline, gentianine, carpine), amino acids, some of which act as insulin secretagogues (i.e. 4-hydroxyisoleucine, arginine), coumarine, mucilaginous fibres, nicotinic acids and other vitamins and minerals^[38]. A good number of antidiabetic works were done on the chemical constituents of *Ficus bengalensis*. Flavonoid constituents isolated from the bark caused hypoglycaemia in normal rabbits^[39]. Ambika and Rao^[40] observed that phytosteroline isolated from the roots of the plant caused maximum fall of blood sugar level equivalent of 81% of tolbutamide after 4 hrs, given per oral to fasting rabbits; injection (i.v.) of 5-7.5 mg/kg showed maximum effect after two hours. Augusti et al. further observed that dimethoxy ether of leucopelargonidin administered per oral (100 mg/kg) caused significant hypoglycaemia associated with rise in serum insulin in both normal and moderately diabetic dogs (alloxanised)^[41]. Dimethylether of leucopelargonidin-3-O- α -L-rhamnoside from *F. bengalensis* in 100 mg/kg on administration to diabetic (alloxanised) rats lowered blood sugar level (up to 12%)^[42]. Similarly, a demethoxy derivative of leucocyanidine-3-O- β -D-galactosyl cellobioside and a glycoside, pelargonidin-3-O- α -L-rhamnoside isolated from the bark of the plant demonstrated significant antidiabetic activity^[43,44]. It was also observed that pinitol (D-chiro-(+)-O-methylinositol) isolated from the methanolic extract of *Bougainvillea spectabilis*, when administered orally (0.01 mg/kg) to normal fasted mice, caused maximum blood sugar lowering by 2 hrs, whereas treatment with pinitol (5 doses) in 72 hrs induced fall in blood sugar in alloxanised mice^[45]. Amellin, which comprises of 3-O-methyllyuteolin and 8-O-glucosylscopaner, an active principle of *Scoparia dulcis* possesses immense antidiabetic efficacy as evaluated from pharmacological and clinical studies^[46].

Flavonoid glycosides (FG 1 and FG 2), isolated from *Phyllanthus fratermus*, at a dose of 100 mg/kg p.o. were found to be hypoglycaemic in alloxanised rats (20 and 25%) at 3 hrs; however, no blood sugar lowering was observed in normal rats^[47]. A neoflavonoid, coutareagenin [5-hydroxy-7-methoxy-4-(3,4-dihydroxyphenyl)-2H-benzo-1-pyran-2-on] isolated

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from *Hintonia latiflora*, exhibited promising antidiabetic efficacy^[48]. Carney et al. isolated a prenylated dibenzofuran, achyrofurane from *Achyrocline satureioides* and studied its hypoglycaemic activity; the natural compound significantly lowered blood glucose levels in rat model for type 2 diabetes, when administered orally at 20 mg/kg weight^[49]. Recently, Akhtar et al. reported significant hypoglycaemic activity of *Alpinia galanga rhizome* and its methanol and aqueous extracts in rabbit models^[50]. The hypo-glycaemic effect in normal rabbits was found to be comparable to gliclazide. Phytochemical investigation of rhizome of the plant already revealed the presence of kaempferide, alpinin, galangin, methyl-cinnamate, cincole, tannins, phlobaphines along with some minerals; hence it is conceivable that one or more (organic and inorganic) of the contents of rhizome might be responsible for its hypoglycaemic activity^[50].

CONCLUSIONS

Diabetes mellitus has already emerged as an alarming disease affecting the health much of an appreciable segment of world population. Though existing methods of treatment of the disease reduces the sufferings to some extent, still it remains inadequate and at the same time is costly, and also associated with a lot of side effects. Hence, there is an urgent need for search of more efficacious drugs with no or minimum side effects; those would have to be cheap and easily available to the general masses. Our keen attention to the nature would lead to new drug discovery. A good number of antidiabetic plants that have been used traditionally for a long period is our hope; studies on the chemical constituents of these plants in this direction as reported so far should boost up the ongoing research.

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