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Review Article

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A Review on Some Potential Traditional Phytomedicine with Antidiabetic Properties

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A B S T R A C T

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. WHO has predicted that the major burden will occur in developing countries? Since ancient times, plants have been an exemplary source of medicine. Ayurveda and other Indian literature mention the use of plants in treatment of various human ailments. India has about 45000 plant species and among them, several thousands have been claimed to possess medicinal properties. Research conducted in last few decades on plants mentioned in ancient literature or used traditionally for diabetes has shown anti-diabetic property. In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. The present paper reviews some of such plants and their products (active, natural principles and crude extracts) that have been mentioned/used in the Indian traditional system of medicine and have shown experimental or clinical anti-diabetic activity. We believe that the list of medicinally important families and plants presented in this review is useful to researchers, as well as practitioners.

Keywords- Diabetes, herbs, hypoglycemic agents, traditional medicines.

Introduction

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter [1]. A number of medicinal plants, traditionally used for over 1000 years named rasayana are present in herbal preparations of Indian traditional health care systems [2]. In Indian systems of medicine most practitioners formulate and dispense their own recipes [3]. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as botanical garden of the world [3]. Studies conducted in India in the last decade have

highlighted that not only is the prevalence of diabetes high but also that it is increasing rapidly in the urban population [4]. It is estimated that there are approximately 33 million adults with diabetes in India. This number is likely to increase to 57.2 million by the year 2025. Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Type I diabetes (insulin dependent) is caused due to insulin insufficiency because of lack of functional beta cells. Patients suffering from this are therefore totally dependent on exogenous source of insulin while patients suffering from Type II diabetes (insulin independent) are unable to respond to insulin and can be treated with dietary changes, exercise and medication. Type II diabetes is the more common form of diabetes constituting 90% of the diabetic population. Symptoms for both diabetic conditions may include: (i) high levels of sugar in the blood; (ii) unusual thirst; (iii) frequent urination; (iv) extreme hunger and loss of weight; (v) blurred vision; (vi) nausea and vomiting; (vii) extreme weakness and tiredness; (viii) irritability, mood changes etc. Though pathophysiology of diabetes remains to be fully understood, experimental evidences suggest the involvement of free radicals in the pathogenesis of diabetes [5] and more importantly in the development of diabetic complications [6–8]. Free radicals are capable of damaging cellular molecules, DNA, proteins and lipids leading to altered cellular functions. Many recent studies reveal that antioxidants capable of neutralizing free radicals are effective in preventing experimentally induced diabetes in animal models [9, 10] as well as reducing the severity of diabetic complications [8].

For the development of diabetic complications, the abnormalities produced in lipids and proteins are the major etiologic factors. In diabetic patients, extra-cellular and long lived proteins, such as elastin, laminin, collagen are the major targets of free radicals. These proteins are modified to form glycoproteins due to hyperglycemia. The modification of these proteins present in tissues such as lens, vascular wall and basement membranes are associated with the development of complications of diabetes such as cataracts, microangiopathy, atherosclerosis and nephropathy [11]. During diabetes, lipoproteins are oxidized by free radicals. There are also multiple abnormalities of lipoprotein metabolism in very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) in diabetes. Lipid peroxidation is enhanced due to increased oxidative stress in diabetic condition. Apart from this, advanced glycation end products (AGEs) are formed by non-enzymatic glycosylation of proteins. AGEs tend to accumulate on long-lived molecules in tissues and generate abnormalities in cell and tissue functions [12, 13]. In addition, AGEs also contribute to increased vascular permeability in both micro and macrovascular structures by binding to specific macrophage receptors. This results in formation of free radicals and endothelial dysfunction. AGEs are also formed on nucleic acids and histones and may cause mutations and altered gene expression.

As diabetes is a multifactorial disease leading to several complications, and therefore demands a multiple therapeutic approach. Patients of diabetes either do not make enough insulin or their cells do not respond to insulin. In case of total lack of insulin, patients are given insulin injections. Whereas in case of those where cells do not respond to insulin many different drugs are developed taking into consideration possible disturbances in carbohydrate-metabolism. For example, to manage post-prandial hyper-glycaemia at digestive level, glucosidase inhibitors such as acarbose, miglitol and voglibose are used. These inhibit degradation of carbohydrates thereby reducing the glucose absorption by the cells. To enhance glucose uptake by peripheral cells biguanide such as metphormine is used. Sulphonylureas like glibenclamide is insulinotropic and works as secretogogue for pancreatic cells. Although several therapies are in use for treatment, there are certain limitations due to high cost and side effects such as development of hypoglycemia, weight gain, gastrointestinal disturbances, liver toxicity etc [14]. Based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable antidiabetic and antioxidant therapy.

Material and methods

Role of phytomedicine in diabetes

Phytomedicine are being looked up once again for the treatment of diabetes. Many conventional drugs have been derived from prototypic molecules in medicinal

plants. Metformin exemplifies an efficacious oral glucose-lowering agent. Its development was based on the use of Galega officinalis to treat diabetes. Galega officinalis is rich in guanidine, the hypoglycemic component. Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued after insulin became more widely available. However, experience with guanidine and biguanides prompted the development of metformin. To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated. Major hindrance in amalgamation of herbal medicine in modern medical practices is lack of scientific and clinical data proving their efficacy and safety. There is a need for conducting clinical research in herbal drugs, developing simple bioassays for biological standardization, pharmacological and toxicological evaluation, and developing various animal models for toxicity and safety evaluation. It is also important to establish the active component/s from these plant extracts.

Table 1 - Some Important Examples of Potential Anti Diabetic Phytomedicine.

Botanical Name	Family	Vernacular	Part(s)	Ethnobotanical Usage
Acacia arabica (Lam.) Willd.	Mimosaceae	Karuvaelai	S	Seeds hypoglycemic
Aegle marmelos (L.) Corr.	Rutaceae	Vilvam	L	Leaf powder with cow's milk is taken orally.
Allium cepa Linn.	Alliaceae	Vengayam	B	Leaf juice with honey or milk and taken orally.
Allium sativum Linn.	Alliaceae	Pundu	B	Leaf, bulb antidiabetic taken orally.
Andrographis lineata Wall. ex Nees.	Acanthaceae	Siriyanangai	L	Leaf powder mixed with cow's milk is taken
Azadirachta indica A. Juss.	Meliaceae	Vembu	L	Leaves anti diabetic.
Bombax ceiba L	Bombacaceae	Elavampanchu	S	Seed powder with goat's milk is taken orally.
Brassica juncea (Linn.) Czern. & Coss.	Bracecaceae	Kadugu	S	Seed powder with milk is taken orally
Cajanus cajan (Linn.) Millsp.	Fabaceae	Thuvarai	S	Seeds cooked and taken along with food.
Catharanthus roseus L. (G) Don.	Apocyanaceae	Nityakalyani	WP	Flower decoction taken orally.
Coccinia indica W & A	Cucurbitaceae	Kovai	F	Leaf / Fruit decoction is taken topically.
Cuminum cyminum Linn.	Apiaceae	Cheerakam	S	Fruit soaked in water

				and taken orally.
Erythrina indica Lam.	Fabaceae	Mulmurungai	L	Leaves consumed to treat diabetics.
Euphorbia antiquorum Linn.	Euphorbiaceae	Chzathura kalli	L	Leaves /fruits consumed to treat diabetics.
Ficus benghalensis Linn.	Moraceae	Alamaram	F	Fruits taken to treat diabetics.
Gymnema sylvestre R.Br.	Apocyanaceae	Sakkaraikolli	L	Leaf made to juice and taken orally.
Hibiscus rosa-sinesis Linn.	Malvaceae	Sembaruthi	L	Tender fresh leaves used to cure diabetes.
Ipomoea batatas (Linn.)	Convolvulaceae	Sakkaraivalli	T	Leaf juice is taken to treat diabetics
Jatropha glandulifera Rox.	Euphorbiaceae	Adalai chedi	T	Tubers boiled and taken to treat diabetics.
Lantana camara Linn.	Verbenaceae	Unni chedi	L/F	Leaf and fruits consumed raw - treat diabetics.
Mangifera indica L.	Anacardiaceae	Ma	S	Dry kernel powder in cow's milk.
Momordica charantia L.	Cucurbitaceae	Pavai	F	Fruit juice is taken to treat diabetics.
Murraya koeingii (L.) Spreng.	Rutaceae	Karuvepalai	L	Leaf juice is taken to treat diabetics.
Murraya koeingii (L.) Spreng.	Rutaceae	Karuvepalai	L	Leaf juice is taken to treat diabetics.
Nelumbo nucifera Gaertn.	Nymphiaceae	Alli	F	Flowers made to juice and taken orally.
Ocimum santum L.	Lamiaceae	Thulasi	L	Leaf powder in honey taken oral.
Punica granatum L.	Punicaceae	Madulai	F	Fruit used to treat diabetics.
Syzygium cumini (L.) Skeels	Myrtaceae	Naval	S	Seeds powder reduce blood sugar/ diabetics
Trigonella foenum-graecum L.	Fabaceae	Vendhyem	S	Seed soaked in water used to treat diabetics

Table 2- The list of potential hypoglycemic plant families, scientific name of the plant, route of administration ,animal used, dose, active ingredient and their effects.

Biological Family	Route of administration	Animal used	Dose	Active ingradient	Effect
Acanthaceae (Asteracantha longifolia)	Oral	alloxan-induced diabetic rabbits	(20 g/kg of starting material)		improve glucose tolerance in healthy human subjects and diabetic patients.
Amaranthaceae (Achyranthes aspera)	Oral	alloxan-induced diabetic rabbits	2, 3, and 4 g/kg	calcium, zinc, magnesium, manganese and copper	significant dose-related hypoglycaemic effect
Anacardiaceae (Mangifera indica)	Oral	Wiztar rats	150mg/kg	Mangiferin, sucrose Xylose, flavonidal tannins	hypoglycaemic action due to a reduction in the intestinal absorption of glucose.
Apiaceae (Daucus carota)	Oral	Male Swiss mice	200mg/kg	Pectin,carotin, extractine gluten, albumen, volatile oil	improve the glucose tolerance.
Apocynaceae (Rhazya stricta)	Oral	streptozotocin-diabetic rats.	0.5, 2.0 and 4.0 g/kg	Alkaloids, flavonoids	glycaemia was reduced by approximately 6, 8 and 30 %, respectively.
Araliaceae (Ginseng Radix)	i.v	adrenaline-induced hyperglycaemic mice	100 mg/kg	Ginseng polypeptides	lowered blood glucose level in diabetic animals.
Chenopodiaceae (Beta vulgaris var.Cicla L.)	Oral	alloxanised diabetic rats	200mg/kg	Betavulgarosides I, II, III, IV, VI, VII, VIII oleanolic acid oligoglycosides	inhibited the increase in the nonenzymatic glycosylation of skin proteins and blood glucose.

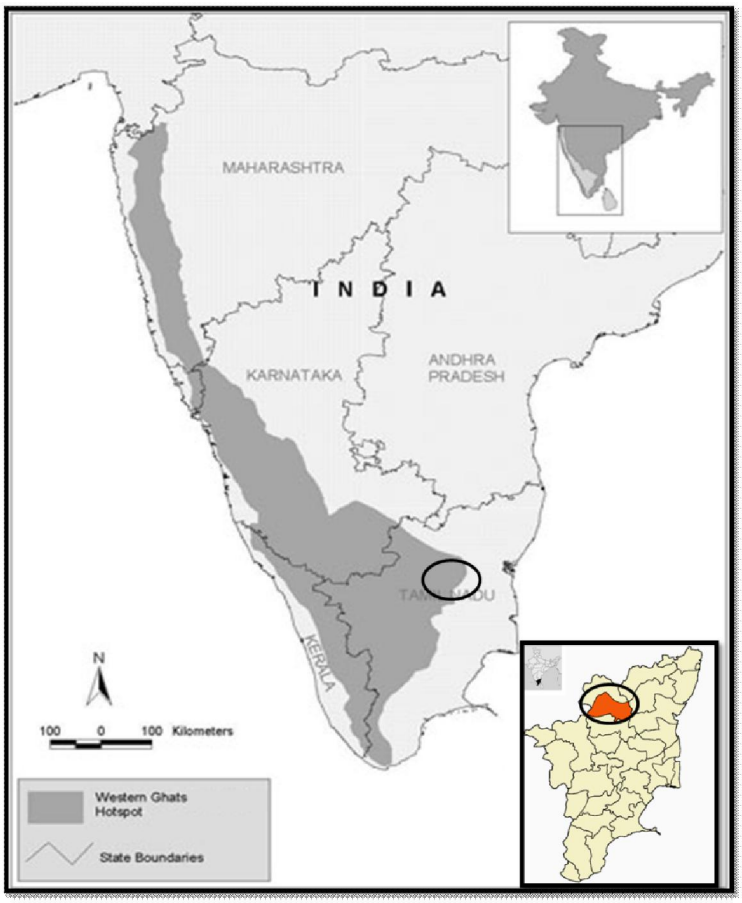
Recent research and reviews

A number of reviews have been published in the last three decades on plants screened for hypoglycemic activity in India [15-31] and elsewhere[27-29]. Very recently, two exhaustive reviews have been published based on global literature survey on 150

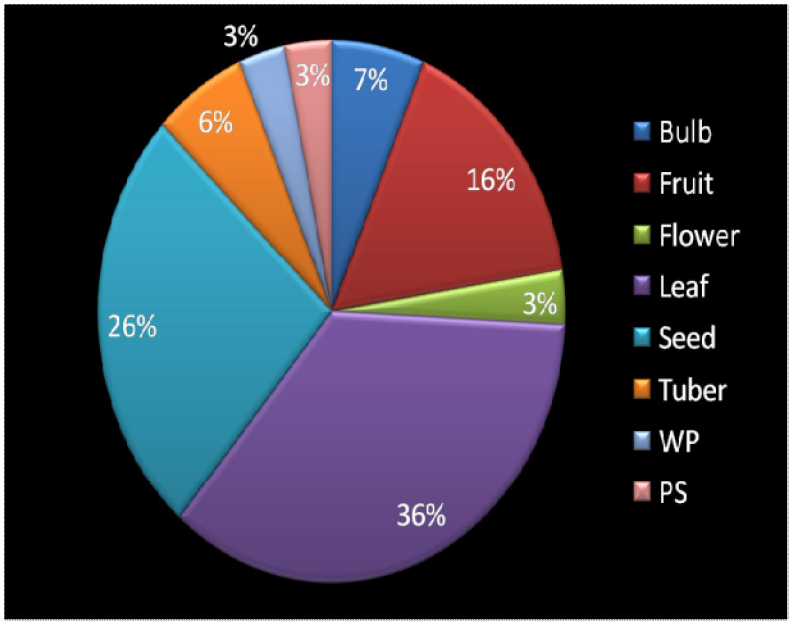
plants[28] and 343 plants[29] from different parts of the world. some plants like
Allium cepa (Onion, piyaj), Allium sativum (garlic, lasun), Syzygium cumini (Syn. Eugenia jambolana; (black plum; jamun), Momordica charantia (bitter gourd; karela) Gymema sylvestre (Gurmar), Pterocarpus marsupium (Vijay-) sar) etc. have attracted more attention of the scientists as well as laymen, in recent years. Only a few of phytomedicine will be discussed here, in" some detail.(Table no1& 2) In most animal studies, water extracts or alcoholic extracts of the plants have been screened. In a few studies, the active principles of plants have been investigated for hypoglycemic activity. In a systematic screening programme of plants available in India over several decades, October, 1989 the Central Drug Research Institute (CDRI), Lucknow (India), reported positive hypoglycemic activity in only 11 plants[56], none of which was considered encouraging enough for being taken up for further studies. Among the major chemical constituents of plants credited with hypoglycemic action are glycosides, alkaloids, glycans, triterpenes, mucilages, polysaccharides, oils, vitamins, saponins, glycoproteins, peptides, amino acids & proteins. Reports on as many as 20 plant mucilages showing hypoglycaemic activity have been reviewed recently[28]. Among these, mucilages isolated from Malavaceous plants which show hypoglycemic activity have been found to have highly interesting chemical structure relating to a trisaccharide structural unit which offer interesting leads on structure-activity relationship. Pharmacological screening for hypoglycemic activity has been done using various animal models like normal, fasting rats & rabbits; alloxan-treated rabbits; hyperglyceraia induced in rats by adrenaline, corticoropin, somatotropin as also by streptozotocin and by pancreatectomy. On plants like Momordica charantia and Pterocarpus mar sup um, some contradictory results have been reported by different groups of Indian workers. M. charantia has revealed hypoglycemic activity in most studies. Thus, the fruit of this plant showed hypoglycemic effect in normal & alloxan-induced diabetic rabbits[38], while M. charantia seeds proved hypoglycemic in streptozotocin-induced diabetes in rabbits in normal rabbits[41], in normal & alloxan diabetic dogs[40], in hyperglycemia induced by anterior pituitary extract in rats[33].In other studies on rabbits, M. charantia juice showed only a mild hypoglycemic effect in normal & alloxan diabetic animals, while proving to be toxic at 10 ml/kg dose[39]. It showed no effect on normal rabbits either on acute or chronic administration[57]. Clear cut data on the actual chemical constituents of bitter gourd which can be held responsible for its hypoglycemic activity arelacking, in spite of a number of reports on charantin (the non-nitrogenous neutral principle) and the polypeptide-p[42] or plant (P)- insulin [43,55] isolated from this plant. Another plant well reputed in Ayurvedic medicine as an anti-diabetic drug and which has also shown considerable promise in initial pharmacological studies is Pterocarpus marsupium. After sporadic studies on various extracts of the plant (between 1959 and 1971) by different group of authors,[34,37,44,45] a series of investigations on rats done at Banaras Hindu University, Varanasi, claimed a novel antidiabetic mechanism of action of the flavonoid isolated from P. marsupium viz. (—) epicatechin- The flavonid (isolated from the plant), as also its synthetic counterpart, were claimed to regenerate the j8-cells of the islets of pancreas in alloxon diabetic rats[33,49,52]. These startling results attributed to (—) epicatechin were, however, not confirmed by other workers from different parts of the world [58-60].

This serves as a familiar example of a few over-enthusiastic scientists jumping to premature conclusions on the identity of 'active principles' as well as a novel mode of action of plant drugs without confirmatory evidence. Despite such setbacks, as the October, 1989 crude, extract of the plant has shown a hypoglycemic effect consistently and the plant continues to be used in clinical practice by Ayurvedic physicians (especially in North India) for the management of diabetes, further studies, are called for on this plant. Gymnema sylvestre is yet another plant reputed specially in South India for its use as an antidiabetic drug. Adrenaline-induced hyperglycemia in rats was countered by injection of the leaf extract [47]. Orally, the leaves significantly reduced the hyperglycemia induced in rats by anterior pituitary extract[46]. In alloxan diabetic rabbits, the leaf extract of the plant reduced the blood sugar level and also

reversed the hepatic changes produced by hyperglycemia [48,51]. The alcohol-water extract of G. sylvestre restored the elevated protein-bound polysaccharide components & glycosaminoglycans in serum & tissues of alloxan diabetic rats, and it was suggested that the plant apparently restores the synthesis of sulfated glyosaminolycans and thereby could be of possible assistance in preventing vascular complications of diabetes [36]. The seeds of Syzygium cumini are used by the Ayurvedic physicians (and also in Indian folklore) in the treatment of diabetes mellitus. The hypoglycaemic activity of the seeds has been studied by several workers in animal models [32,35,54]. In alloxan diabetic rats, S. cumini seed extract led to a decrease in the levels of blood glucose, urea and serum triglyceride levels [50,53]. The botanical identity of certain plants used by Ayurvedic clinicians is known to be controvertial. One such example is of the drug 'Saptarangi' famed in Ayurveda as an antidiabetic agent. This plant was screened for hypoglycaemic activity under the Composite Drug Research Scheme (CDRS) of the Indian Council of Medical Research during 1965-69. In the initial part of the study, the drug 'Saptarangi' was botanically identified as Caeseria esculenta. However, the commercially available Saptarangi was subsequently correctly identified as Salacia prenoides (yellow variety) and Salacia macrosperma (brown variety). S. prenoides (aqueous extract) evinced hypoglycemic activity comparable to tolbutamide in glucose tolerance tests in male rabbits [61]. This experience illustrates and emphasizes the vital need for authentic botanical identification of the plants before embarking on chemical and biological studies. Some known antidiabetic potential phytomedicine are listed in Table no 2 and is best used only as a preliminary screening of potential antidiabetic plants, not as a definitive or complete list of hypoglycemic plants.



Sketch map of the area of most of the drugs discussed.



Percentage distribution analysis of anti-diabetic remedies obtained from different plant parts.

Conclusion

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. WHO has predicted that the major burden will occur in developing countries. Studies conducted in India in the last decade have highlighted that not only is the prevalence of diabetes high but also that it is increasing rapidly in the urban population. It is estimated that there are approximately 33 million adults with diabetes in India. This number is likely to increase to 57.2 million by the year 2025. Phytomedicine are being looked up once again for the treatment of diabetes. Many conventional drugs have been derived from prototypic molecules in medicinal plants. We believe that the list of medicinally important families and plants presented in this review is useful to researchers, as well as practitioners.

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