Current update on anti-diabetic biomolecules from key traditional Indian medicinal plants

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Diabetes is a growing health concern worldwide and now emerging as an epidemic world over. The management of diabetes is still a major challenge. Thus there is great demand for research on natural products with anti-diabetic properties. Numerous studies have confirmed the benefits of medicinal plants with anti-hyperglycemic effects in the management of diabetes mellitus. In this review, we address the beneficial effects of selective medicinal plant species such as *Allium cepa, Allium sativum, Aloe vera, Azadirachta indica, Gymnema sylvestre, Syzygium cumini* and *Pterocarpus marsupium,* and emphasize on the role of active biomolecules which possess anti-diabetic activity.

Keywords: Anti-diabetic, biomolecules, diabetes, hyperglycemia, medicinal plants.

DIABETES is a chronic metabolic disorder that poses a major challenge worldwide. Currently in India the number of people with diabetes is around 40.9 million and it is expected[1] to rise to 69.9 million by 2025. India has emerged as the diabetic capital of the world[2]. Unless urgent preventive steps are taken, it will become a major health problem. The Indian Diabetes Federation (IDF) estimated 3.9 million deaths for the year 2010, which represented 6.8% of the total global mortality[3].

Traditional anti-diabetic plants might provide new oral anti-diabetic compounds, which can counter the high cost and poor availability of the current medicines for many rural populations in developing countries[4]. Plant drugs are frequently considered to be less toxic and free from side effects than synthetic ones[5]. In India, indigenous remedies have been used in the treatment of diabetes mellitus since the time of Charaka and Sushruta (6th century BC)[6]. 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. India is the largest producer of medicinal herbs endowed with a wide diversity of agro-climatic conditions and is called as botanical garden of the world[7]. Pharmacological and clinical trials of medicinal plants have shown anti-diabetic effects and repair of β-cells of islets of Langerhans[8].

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Concurrently, phytochemicals identified from traditional medicinal plants present an exciting opportunity for the development of new types of therapeutics. Phytochemicals can offer a new avenue to greatly impact the onset and progression of chronic diseases, oxidant stress and ageing. The phytoprotectants act as bioenhancers of several physical and biochemical processes[9].

This review mainly focuses on the role of the biomolecules from a few Indian traditional medicinal plants with anti-diabetic potential with diverse chemical structures. Unlike synthetic molecules, little work has been done on the phytocompounds as their isolation procedure is complex, it is difficult to ascertain their structures and sometimes biological activities are lost during establishing their structure and function relationship with respect to the drug target. However, it is imperative that their clinical and pharmacological studies should be conducted rigorously to exploit the potential of these plant molecules.

Role of Indian medicinal plants in the treatment of diabetes

The plant kingdom has become a target for the search of biologically active lead compounds by multinational drug companies. Many of these medicinal plants and herbs are also part of our diet as spices, vegetables and fruits. They are a potential source of many drugs used in modern medicine, for example, quinine, opium alkaloids, atropine, cardiac glycosides (digitalis) and the popular hypoglycemic drug glucophage (metformin), derived from *Galega officinalis*[10]. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. The following traditional Indian medicinal plants are described chronologically.

Allium cepa Linn. (family: Liliaceae), pyaj (Hindi); onion (common name).
Allium sativum Linn. (family: Alliaceae), lahasun (Hindi); garlic (common name).
Aloe vera (Linn.) Burm. (syn. *Aloe barbadensis* Miller) (family: Aloaceae), ghee kunwar (Hindi); aloe (common name).
Azadirachta indica A. Juss. (family: Meliaceae), neem (Hindi); Indian lilac tree or neem (common name).

Gymnema sylvestre R. Br. (family: Ascelpiadaceae), gudmar (Hindi); periploca of the woods (common name). *Syzygium cumini* Linn. (syn. Eugenia jambolana (L.) (family: Myrtaceae), jamun (Hindi); blackberry (English). *Pterocarpus marsupium* Roxb. (family: Fabaceae), vijayasar (Hindi); Indian kino tree (English).

Active hypoglycemic constituents from plants

A wide and diverse range of plants have been reported in the literature to prevent and treat diabetes. Several phytochemicals, including alkaloids, flavonoids, glycosides, glycolipid, galactomannan, polysaccharides, peptidoglycan, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids, saponins, dietary fibres and inorganic ions affect various metabolic cascades, which directly or indirectly affect the level of glucose in the human body[6]. These have produced potent hypoglycemic, anti-hyperglycemic and glucose suppressive activities[11]. The above effects achieved by either increase in serum insulin level or increase in the production of insulin from pancreatic β-cells, inhibit glucose absorption in the gut, stimulate glycogenesis in liver or increase glucose utilization by the body[6,12,13]. These compounds also exhibit their antioxidant, hypolipidemic, anticataract activities, restored enzymatic functions, repair and regeneration of pancreatic islets and alleviation of liver and renal damage[14].

A few traditional Indian anti-diabetic plants and their beneficial effects have been studied in various models of experimental diabetes like mice, rats and rabbits with the dosage of different plant parts; the period of study varied between 24 h and 45 days. The data are summarized in Table 1. Limited relevant clinical studies substantiate the anti-diabetic activities of these plants. The active molecules with structures from these plants used for treating hyperglycemia are summarized in Table 2. Administration of sulphur-containing amino acids, namely S-methyl cysteine sulfoxide (SMCS) and diallyl thiosulfinate isolated from the plants *Allium cepa*[15–18] and *Allium sativum*[19–21] to alloxan-induced diabetic rats activates the enzymes hexokinase, glucose-6-phosphatase, 3-hydroxy-3-methyl-glutaryl (HMG) Co-A reductase and lecithin-cholesterol acyltransferase (LCAT). S-allyl cysteine (SAC), a sulphur-containing amino acid derived from *A. sativum*[22,23], may constitute an alternative to insulin as both long- and short-term treatments with this compound correct the hyperglycemia that occurs in diabetic model[24–26].

The mechanism by which *A. cepa* and *A. sativum* might work is through the inhibition of dipeptidyl peptidase-4 (DPP-4), which has amino and hydroxyl groups as shown in Figure 1 *b* and *c*. DPP-4 inhibitors (sitagliptin, vildagliptin, alogliptin, etc.) have emerged as a new class of anti-diabetic agents that increase insulin secretion and reduce glucagon secretion by preventing the inactivation of glucagon-like peptide-1 (GLP-1), thereby lowering glucose levels. One is = O which binds to glutamic aid side chain and other is NH_2 group that binds to tyrosine side chain[27,28]. Several DPP-4 inhibitors are commercially available either as stand-alone or in combination with metformin.

Aloe vera contains polysaccharides which increase the insulin level and show hypoglycemic properties[29]. The five phytosterols of *A. vera*, lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol and 24-methylene-cycloartanol showed anti-diabetic effects in type-2 diabetic mice[30] (Table 2).

Saponins are glycosides of steroids or triterpinoids found in plants. β-Sitosterol, a steroid found in *A. indica*[31], and gymnemic acid IV isolated from *Gymnema sylvestre* exhibited potent hypoglycemic activity in animal models[32,33] (Table 2). Various hypoglycemic principles of *G. sylvestre* isolated from the saponin fraction of the plant are referred to as gymnemosides and gymnemic acids[34,35]. Gymnemic acids I to VII and gymnemosides a to f[36] as well as protein-bound polysaccharide components and glycosaminoglycans were isolated and administrated to diabetic animals and humans. Gymnemic acids III, IV, V, VII and gymnemosides b were identified as the anti-hyperglycemic active constituents. The reduced glucose levels are exerted by the crude extract due to the presence of dihydroxy gymnemic triacetate, which has the ability to release insulin by the stimulation of a regeneration process and revitalization of the remaining β cells[37,38].

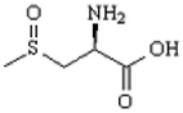
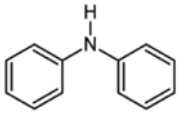
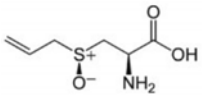
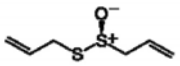
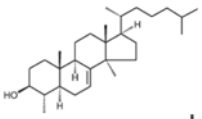
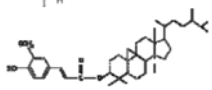
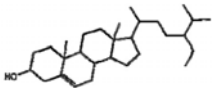
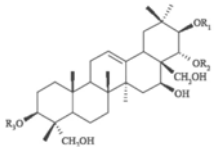
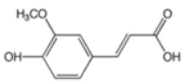
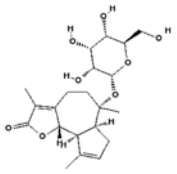
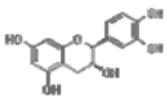
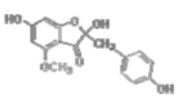
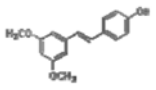
Flavonoids are a group of naturally occurring compounds which possess hypoglycemic and antioxidant properties. Some flavonoids have hypoglycemic properties because they improve altered glucose and oxidative metabolism of the diabetic states[39]. Bhavna *et al.*[40] reported that flavonoid-rich extract from the seeds of *Eugenia jambolana* possesses significant hypoglycemic and hypolipidemic activities in streptozotocin-induced diabetic rats. Mandal *et al.*[41] reported that the ferulic acid (phenolic acid), an ethereal fraction of ethanolic extract of *S. cumini* seeds, shows significant anti-diabetic activity (Table 2). Cuminoside (phenolic glycoside), isolated from the methanolic extract of *S. cumini* seeds, has significant hypoglycemic and antioxidant potential in STZ-induced diabetic rats[42]. Pari and Satheesh[43] reported pterostilbene (phenolic compound) as the main constituent of *P. marsupium* which might contribute to its anti-diabetic action (Table 2).

Hence it is demonstrated that medicinal plants have potential effectiveness against diabetes and the photochemicals play a major role in the management of diabetes. The toxic effects and pharmacological activities of these plants should also be elucidated. Available data on anti-diabetic response of these herbs suggest that there are many active ingredients present in different parts of these herbs, which in turn act through different pathways and

Table 1. Plant species used as an anti-diabetic and their wide pharmacological effects experimentally observed using crude extracts and pure compounds

Plant	Part used	Photograph	Pharmacological activity as antidiabetic	Dose	Model used	Reference
Allium cepa L. (onion) Family: Liliaceae	Bulb		• S-methyl cysteine sulfoxide (SMCS) showed antidiabetic and hyperlipidemic activity	200 mg/kg body weight (BW) of SMCS	Alloxanized rats	15
			• Anti-hyperglycemic and anti-hyperlipidemic activity	200 mg/kg BW of SMCS	High cholesterol diet-fed rats	16
			• Anti-hyperglycemic and insulin resistance in high fat diet	2% freeze dried powder	STZ rats	17
Allium sativum L. (garlic) Family: Alliaceae	Cloves		• S-allyl cysteine (SACS) showed beneficial effect on antioxidant system	150 mg/kg BW of SACS	STZ rats Alloxanized rats	19
			• SACS showed anti-diabetic activity	200 mg/kg BW of SACS	Fructose-induced hyperinsulinemic hyperlipedemic, hypertensive rats	20, 21 45
			• Allicin lowered the blood pressure and improved lipid profile in hyperlipidemic, hyperinsulinemic	8 mg/kg BW of allicin		
			• Anti-diabetic activity	0.5 mg/kg BW of ethanolic extract	STZ rats	46
Aloe vera (L.) Burm.f. (aloe) Family: Aloaceae	Leaf		• Anti-hyperglycemic activity with protective effect on pancreas, liver and small intestine	300 mg/kg BW of ethanolic extract	STZ rats	4
				500 mg/kg BW of dried sap	Alloxanized mice	47
				300 mg/kg BW of ethanolic extract	STZ rats	48
			• Hypoglycemic effect of aloe			
			• Hypoglycemic activity	300 mg/kg BW of Ethanolic extract	Alloxanized rabbits	49
			• Hypoglycemic and reduced HbA1c			
Azadirachta indica A. Juss. (neem) Family: Meliaceae	Leaf and seed		• Hypoglycemic activity	Hydro alcoholic extract	STZ rats	50, 51
			• Hypoglycemic and restricted oxidative stress	2 mg/kg BW of petroleum ether extract of seed kernel	STZ rats	52, 53
			• Anti-hyperglycemic activity			
			• Reduced intestinal glucosidase activity and anti-hyperglycemic properties	250 mg/kg BW of crude ethanol extract	Alloxanized rabbits	54, 55
				100 µg of chloroform leaf extract	STZ mice	56, 57
Gymnema sylvestre (Periploca of the woods) Family: Ascelpiadaceae	Leaf		• Anti-diabetic activity	200 mg/kg BW of methanol extract	Alloxanized rats	8
			• Anti-hyperglycemic effect	Powdered leaves	Beryllium nitrate-treated rats	58
			• Hypolipidemic effect in hypertensive rats	1.6% w/w of 25% gymnemic acid content		
					Spontaneously hypertensive rats	59
Syzygium cumini Walp. (Eugenia jambolana) (blackberry) Family: Myrtaceae	Seed and pulp		• Hypoglycemic and anti-oxidant activity	2.5 and 5 g/kg BW of aqueous seed extract	Alloxanized rats	60
			• Hypoglycemic activity	500 mg/kg BW of seed powder	STZ rats	61
			• Anti-hyperglycemic effect	25 mg/kg BW of water and ethanolic extract of fruit pulp	Alloxanized rabbits	62
			• α-Glucosidase inhibitory activity	250 mg/kg BW of seed kernel acetone extract	Goto–Kakizaki rats	63
Pterocarpus marsupium Roxb. (Indian kino tree) Family: Fabaceae	Bark		• Anti-diabetic and protective effect on serum protein, ALP and ACP, albumin levels and HbA_{1c}	300 mg/kg of methanolic extract	STZ rats	64
					STZ rats	65
			• Anti-hyperglycemic activity	0.25 g/kg BW of ethanol extract		66, 67
			• Hypoglycemic activity	250 mg/kg BW of aqueous extract	Alloxanized rats	
			• Hepatoprotective effect	25 mg/kg of methanol extract	Wistar rats	68

Table 2. Plant species and their active molecules with structures used for treating hyperglycemia and validated for anti-diabetic properties

Plant	Structure of the active phytoconstituents having anti-diabetic potential/s	Active constituent	Potential beneficial effects	Dose	Model used	Reference
Allium cepa L. Family: Liliaceae		SMCS	• Hypoglycemic, hyperlipidemic and antioxidant activity	200 mg/kg BW of SMCS 0.5% of freeze-dried onion powder	Alloxanized rats High-fat diet STZ rats alloxanized rats	15 17 69
		Diphenylamine	• Anti-hyperglycemic activity	SMCS Diphenylamine	Glucose-fed rabbits	70
Allium sativum Linn. (Family: Alliaceae)		SACS	• Anti-hyperglycemic and antioxidant activity	200 mg/kg BW of SACS	Alloxanized rats	21
		Allicin (diallyl thiosulfinate)	• Anti-hyperglycemic activity	8 mg/kg BW of allicin 250 mg/kg of allicin	Fructose-induced hyperinsulinemic, hyperlipidemic, hypertensive rats Alloxanized rats	23, 45
Aloe vera (Linn.) Burm. f. (Syn. *Aloe barbadensis* Miller) (Family: Aloaceae)		Lophenol (phytosterols)	• Anti-hyperglycemic effects	1 µg/mouse of lophenol, 24-methylene cycloartanol	Lepr$^{db/J}$ (*db/db*) mice	30
		24-Methylene-cycloartanol				
Azadirachta indica A. Juss. (Family: Meliaceae)		β-Sitosterol (steroid)	• Anti-hypoglycemic activity	β-Sitosterol	Type-2 diabetic rat model	31
Gymnema sylvestre R. Br. (Family: Ascelpiadaceae)		Gymnemic acids IV (R_1 = tigloyl, R_2 = H, R_3 = glucuro-pyranosyl)	• Anti-hypoglycemic activity	13.4 mg/kg BW of gymnemic acids IV	STZ mice STZ rats	32, 33
Syzygium cumini Linn. (Syn. Eugenia jambolana (L.) (Family: Myrtaceae)		Ferulic acid (phenolic acid)	• Anti-diabetic activity	Ethereal fraction of the ethanolic extract of the seed	STZ rats	41
		Cuminoside (phenolic glycoside)	• Anti-hypoglycemic and antioxidant activity	50 mg/kg BW of cuminoside	STZ rats	42
Pterocarpus marsupium Roxb. (Family: Fabaceae)		(–)-Epicatechin (flavonoid)	• Anti-hyperglycemia and insulinogenic activity	30 mg/kg BW of epicatechin	Alloxanized rats STZ rats	71
		Marsupsin and pterostilbene (phenolic constituents)	• Anti-hyperglycemic activity	40 mg/kg of pterostilbene	STZ-nicotinamide rats	43, 72
						

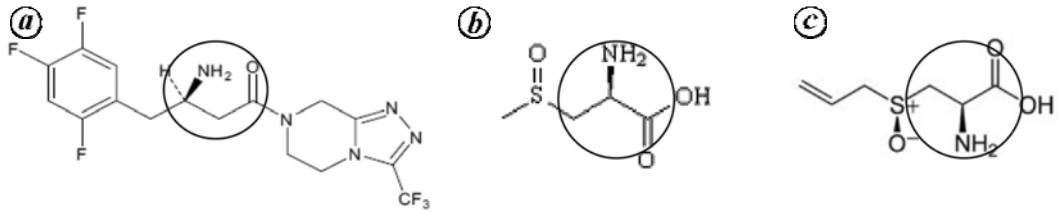


Figure 1. (***a***) Structure of sitagliptin and its electrophilic group involved in the inhibition of DPP-4. Similar structures in *Allium cepa* (***b***) and *Allium sativum* (***c***) which may bind to active site of DPP-4 inhibitors.

have a role in many diseases apart from diabetes. Moreover, they can provide a new type of chemotypes which will help phytochemists and can offer potential for cost-effective management of diabetes through dietary interventions, nutrient supplementation and combination therapies with synthetic drugs in the short term and as the sole medication from natural sources over the long term[44].

Future direction

Although many plant species have been validated for their anti-diabetic properties and related complications, there is a need for modern research in the identification of phytochemical compound(s), their target(s) and their modes of action and combination therapy of plant products with synthetic drugs. To make the therapy cost-effective, extensive clinical studies for long-term side-effects are a must. A large-scale production of quality plant material and innovative procedures to easily consume these medicinal plant species have to be further validated.

Conclusion

This review discussed selective medicinal plant species from India and showed that they have anti-diabetic activity. In addition, many of these species have a phenolic content, phytosterols, saponins and flavonoids. However, an overall ranking of the anti-diabetic strength of these species cannot be determined because of the different experimental methods used in various studies. We have focused on plants belonging to several different families to understand their therapeutic use and their potential anti-diabetic activities. It requires biological testing of plant extracts, isolation of bioactive components, as well as toxicological, pharmacodynamical and, ultimately, clinical studies. Indian medicinal preparations are often considered being effective due to a mixture of active ingredients rather than a single constituent. To make herbal therapies more effective, it is pertinent to isolate anti-diabetic molecules, define their targets for understanding their modes of action, and establish structure and function relationship for better efficacy and pharmacokinetic profile. Prevention of diabetes is our most powerful intervention and successful implementation of these proven strategies should be the focus of our efforts. In future, these efforts will lead to new chemotypes which will be safer and more cost-effective for the rural Indian population suffering from diabetes, whose numbers are increasing linearly.

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