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 expected1 to rise to 69.9 million by 2025. India has emerged as the diabetic capital of the world2. 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 mortality3.

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 countries4. Plant drugs are frequently considered to be less toxic and free from side effects than synthetic ones5. 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 world7. Pharmacological and clinical trials of medicinal plants have shown anti-diabetic effects and repair of β-cells of islets of Langerhans8.

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 processes9.

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 officinalis10. 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).
**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. These have produced potent hypoglycemic, anti-hyperglycemic and glucose suppressive activities. 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. These compounds also exhibit their antioxidant, hypolipidemic, antitumor activities, restored enzymatic functions, repair and regeneration of pancreatic islets and alleviation of liver and renal damage.

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* and *Allium sativum* 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*, may constitute an alternative to insulin as both long- and short-term treatments with this compound correct the hyperglycemia that occurs in diabetic model.

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 1b 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 acid side chain and other is NH₂ which binds to tyrosine side chain. 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. The five phytosterols of *A. vera*, lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartenol and 24-methylene-cycloartenol showed anti-diabetic effects in type-2 diabetic mice. *Gymnema sylvestre* exhibited potent hypoglycemic activity in animal models (Table 2). Various hypoglycemic principles of *G. sylvestre* isolated from the saponin fraction of the plant are referred to as gymnemosides and gymnemic acids. Gymnemic acids I to VII and gymnemosides a to f 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.

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. Bhavna et al. 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. 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 seeds, shows significant anti-diabetic activity in type-2 diabetic rats. Pari and Satheesh reported pterostilbene (phenolic compound) as the main constituent of *P. marsupium* which might contribute to its anti-diabetic action (Table 2).
<table>
<thead>
<tr>
<th>Plant</th>
<th>Part used</th>
<th>Photograph</th>
<th>Pharmacological activity as anti-diabetic</th>
<th>Dose</th>
<th>Model used</th>
<th>Reference</th>
</tr>
</thead>
</table>
| *Allium cepa* L. (onion) | Bulb          | ![Image](image1) | • S-methyl cysteine sulfoxide (SMCS) showed anti-diabetic and hyperlipidemic activity  
• Anti-hyperglycemic and anti-hyperlipidemic activity  
• Anti-hyperglycemic and insulin resistance in high fat diet | 200 mg/kg body weight (BW) of SMCS | Alloxanized rats  | 15        |
| *Allium sativum* L. (garlic) | Cloves        | ![Image](image2) | • S-allyl cysteine (SACS) showed beneficial effect on antioxidant system  
• SACS showed anti-diabetic activity  
• Allicin lowered the blood pressure and improved lipid profile in hyperlipidemic, hyperinsulinemic | 150 mg/kg BW of SACS, 150 mg/kg BW of SACS, 8 mg/kg BW of allicin | STZ rats, Alloxanized rats | 19, 20, 21 |
| *Aloe vera* (L.) Burm.f. (aloe) | Leaf          | ![Image](image3) | • Anti-diabetic activity  
• Anti-hyperglycemic activity with protective effect on pancreas, liver and small intestine  
• Hypoglycemic effect of aloe  
• Hypoglycemic and reduced HbA1c | 0.5 mg/kg BW of ethanolic extract, 300 mg/kg BW of ethanolic extract, 500 mg/kg BW of dried sap, 300 mg/kg BW of ethanolic extract | STZ rats, Alloxanized mice, STZ rats | 4, 19, 44 |
| *Azadirachta indica* A. Juss. (neem) | Leaf and seed | ![Image](image4) | • Hypoglycemic activity  
• Hypoglycemic and restricted oxidative stress  
• Anti-hyperglycemic activity  
• Reduced intestinal glucosidase activity and anti-hyperglycemic properties | Hydro alcoholic extract, 2 mg/kg BW of petroleum ether extract of seed kernel, 250 mg/kg BW of crude ethanol extract, 100 μg of chloroform leaf extract | STZ rats, STZ rats, Alloxanized rabbits, STZ mice | 50, 51, 54, 55 |
| *Gymnema sylvestre* (Periploca of the woods) | Leaf          | ![Image](image5) | • Anti-diabetic activity  
• Anti-hyperglycemic effect  
• Hypolipidemic effect in hypertensive rats | 200 mg/kg BW of methanol extract, Powdered leaves, 1.6% w/w of 25% gymnemic acid content | Alloxanized rats, Beryllium nitrate-treated rats, Spontaneously hypertensive rats | 8, 58, 59 |
| *Syzygium cumini* Walp. (Eugenia jambolana) (blackberry) | Seed and pulp | ![Image](image6) | • Hypoglycemic and anti-oxidant activity  
• Hypoglycemic activity  
• Anti-hyperglycemic effect  
• α-Glucosidase inhibitory activity  
• Anti-diabetic and protective effect on serum protein, ALP and ACP, albumin levels and HbA1c  
• Anti-hyperglycemic activity  
• Hypoglycemic activity  
• Hepatoprotective effect | 2.5 and 5 g/kg BW of aqueous seed extract, 500 mg/kg BW of seed powder, 25 mg/kg BW of water and ethanolic extract of fruit pulp, 250 mg/kg BW of seed kernel acetone extract, 300 mg/kg of methanolic extract, 0.25 g/kg BW of ethanol extract, 250 mg/kg BW of aqueous extract, 25 mg/kg of methanol extract | Alloxanized rats, STZ rats, Alloxanized rabbits, STZ rats | 60, 61, 63, 66, 67, 68 |
### Table 2. Plant species and their active molecules with structures used for treating hyperglycemia and validated for anti-diabetic properties

<table>
<thead>
<tr>
<th>Plant</th>
<th>Structure of the active phytoconstituents having anti-diabetic potential/s</th>
<th>Active constituent</th>
<th>Potential beneficial effects</th>
<th>Dose</th>
<th>Model used</th>
<th>Reference</th>
</tr>
</thead>
</table>
| *Allium cepa* L.                   | SMCS                                                                       | Diphenylamine      | • Hypoglycemic, hyperlipidemic and antioxidant activity  
• Anti-hyperglycemic activity     | 200 mg/kg BW of SMCS  
0.5% of freeze-dried onion powder SMCS  
Diphenylamine                      | Alloxanized rats  
High-fat diet  
STZ, rats  
alloxanized rats                    | 15  
17  
69                                    |
| *Allium sativum* Linn. (Family: Alliaceae) | SACS                                                                      | Allicin (diallyl thiosulfinate) | • Anti-hyperglycemic activity  
• Anti-hyperglycemic activity       | 200 mg/kg BW of SACS  
8 mg/kg BW of allicin  
250 mg/kg of allicin                  | Alloxanized rats  
Fructose-induced hyperinsulinemic, hyperlipidemic, hypertensive rats | 21  
23, 45                                |
| *Aloe vera* (Linn.) Burm. f. (Syn. Aloe barbadensis Miller) (Family: Aloaceae) | Lophenol (phytosterols)  
24-Methylene-cycloartanol           |                    | • Anti-hyperglycemic effects  
• Anti-diabetic activity  
• Anti-hypoglycemic activity  
• Anti-hypoglycemic and antioxidant activity | 1 μg/mouse of lophenol, 24-methylene cycloartanol | Leprdb/J (db/db) mice  
Alloxanized rats  
STZ rats  
STZ- nicotinamide rats               | 30  
31  
41  
42                                    |
| *Azadirachta indica* A. Juss. (Family: Meliaceae) | β-Sitosterol (steroid)  
Gymnemic acids IV (R₁ = tigloyl, R₂ = H, R₃ = glucuro-pyranosyl) |                    | • Anti-hypoglycemic activity  
• Anti-hypoglycemic activity   | 13.4 mg/kg BW of gymnemic acids IV | STZ mice  
STZ rats  
STZ rats                             | 32, 33  
31                                    |
| *Gymnema sylvestre* R. Br. (Family: Asclepiadaceae) | Ferulic acid (phenolic acid)  
Cuminoside (phenolic glycoside)    |                    | • Anti-diabetic activity  
• Anti-hypoglycemic and antioxidant activity | Ethereal fraction of the ethanolic extract of the seed | STZ rats   | 41  
42                                    |
| *Syzygium cumini* Linn. (Syn. Eugenia jambolana (L.) (Family: Myrtaceae) | (–)-Epicatechin (flavonoid)  
Marsupsin and pterostilbene (phenolic constituents) |                    | • Anti-hyperglycemia and insulinoenic activity  
• Anti-hyperglycemic activity     | 30 mg/kg BW of epicatechin  
40 mg/kg of pterostilbene           | Alloxanized rats  
STZ rats  
STZ-nicotinamide rats                | 71  
43, 72                               |
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.

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.

References

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