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Optimize Diabetes by Herbal Medicine: A Review

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Plant-based medicinal products have been acknowledged since ancient times and several medicinal plants and their products have been used to control diabetes in the traditional medicinal systems of many cultures worldwide. Several synthetic oral hypoglycemic agents are the primary forms of treatment for diabetes. However, prominent side-effects of such drugs are the main reason for an increasing number of people seeking alternative therapies that may have less severe or no side effects but little toxicological information exists concerning traditional antidiabetic plants. The present paper is an attempt to list the plants with anti-diabetic and related beneficial effects originating from different parts of the world and polyhedral formulations. History has shown that medicinal plants have been used in traditional healing around the world for a long time to treat diabetes; this is because such herbal plants have hypoglycemic properties and other beneficial properties, as reported in scientific literature. There are some such plants described in this review, which clearly shows the importance of herbal plants and polyhedral formulations in the treatment of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and provide a rich source of antioxidants that are known to prevent/delay different diseased states.

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1. INTRODUCTION

Diabetes mellitus is a heterogeneous metabolic disorder characterized by altering carbohydrate, lipid and protein metabolism caused by insulin deficiency, often combined with insulin resistance [1]. It is considered as one of the five leading causes of death in the world [2]. About 150 million people are suffering from diabetes worldwide and it was almost five times more than the estimated ten years ago and this may be doubled by the year 2030 [3]. Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drugs continues because the existing synthetic drugs have several limitations. The herbal drugs with antidiabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine. The plants provide a potential source of hypoglycemic drugs because many plants and plant derived compounds have been used in the treatment of diabetes. Many Indian plants have been investigated for their beneficial use in different types of diabetes and reports occur in numerous scientific journals. Ayurveda and other traditional medicinal system for the treatment of diabetes, describe a number of plants used as herbal drugs. Hence, they play an important role as an alternative medicine due to less side effects and low cost. The active principles present in medicinal plants have been reported to possess the pancreatic beta cells re-generating, insulin releasing and fighting the problem of insulin resistance. Hyperglycemia is involved in the etiology of development of diabetic complications. Hypoglycemic herbs increase insulin secretion, enhance glucose uptake by adipose or muscle tissues and inhibit glucose absorption from the intestine and glucose production from liver [4]. Insulin and oral hypoglycemic agents like sulphonylureas and biguanides are still the major players in the management, but there is a quest for the development of more effective anti-diabetic agents [5].

Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose re absorption is exceeded, glucose spills over into the urine (glycosuria) and causes an osmotic diuresis (polyuria), which in turn, results in dehydration, thirst and increased drinking (polydipsia). Insulin deficiency causes wasting through increased breakdown and reduced synthesis of proteins.

2. VARIOUS FORMS OF DIABETES MELLITUS

I. General-genetic and other factors not precisely defined [4].

a) Type 1 diabetes mellitus (TIDM OR IDDM).

- Type 1A – Auto-immune type 1 diabetes mellitus.
- Type 1B – Non-auto-immune or idiopathic type 1 diabetes mellitus.

b) Type 2 diabetes mellitus (T2DM OR NIDDM).

II. Specific defines gene mutations

a) Maturity onset diabetes of the young (MODY)

- MODY 1 (Hepatic nuclear fact 4-α gene mutations)
- MODY 2 (Glucokinase gene mutations)
- MODY 3 (Hepatic nuclear fact 1-α gene mutations)
- MODY 4 (Pancreatic determining fact x gene mutations)
- MODY X (Unidentified gene mutations(s))

b) Maternally inherited diabetes and deafness (MIDD)
c) Mitochondrial leucine t–RNA gene mutations
d) Insulin gene mutation
e) Insulin receptor gene mutations

III. Diabetes secondary to pancreatic disease

- Chronic pancreatitis
- Surgery
- Tropical diabetes (chronic pancreatitis associated with nutritional and or toxic factors)
- Gestational diabetes

IV. Diabetes secondary to other Endocrinopathies

- Cushing's disease

- Glucocorticoid administration
- Acromegaly

V. Diabetes secondary to immune suppression

VI. Diabetes associated with genetic syndromes eg: Prader–Willi syndrome

VII. Associated with diabetes drug therapy

a) Drugs with Hypoglycemic effects β-Adrenergic receptor antagonists, Salicylates, Indomethacin, Clofibratemand ACE inhibitor.
b) Drugs with Hyperglycemic effects

Epinephrine, Glucocorticoid, β-adrenergic receptor agonist, Calcium channel blockers, Phenytoin and H_2 receptor blocker

Virtually all forms of diabetes mellitus are caused by a decrease in the circulating concentration of insulin (insulin deficiency) and a decrease in the response of peripheral tissues to insulin (insulin resistance). These abnormalities lead to alterations in the metabolism of carbohydrates, lipids, ketones and amino acids. The central feature of the syndrome is hyperglycemia characterized by a high blood glucose concentration.

Hyperglycemia may become toxic and fatal as a result of accumulation of non-enzymatically glycosylated products and osmotically active sugar alcohols such as sorbitol in tissues, the effects of glucose on cellular metabolism also may be responsible [6]. Diabetic ketoacidosis is an acute emergency which develops on prolonged hyperglycemia and develops in the absence of insulin because of an accelerated fat breakdown to acetyl CoA, which in the absence of aerobic carbohydrate metabolism is converted to acetoacetatae, β-hydroxybutyracetone, that causes acidosis [7]. Hemoglobin undergoes glycosylation on its amino–terminal Valine residue to form the glucosyl Valine adducts of hemoglobin, termed hemoglobin A1c. The half-life on the modified hemoglobin is equal to that of the erythrocytes (about 120 days). Since the amount of glycosylated protein formed is proportional to the glucose concentration and the time of exposure of the protein to glucose, the concentration of hemoglobin, A1c in the circulation reflects the severity of the glycemic state [4].

2.1 COMPLICATIONS OF THE DISORDER

Most diabetes complications arise from prolonged exposure of tissues to elevated glucose levels. These complications develop as a consequence of the metabolic derangements in diabetes, often over many years. Many of these result in diseases of blood vessels, either large (macro vascular disease) or small (microangiopathy). Macro vascular disease consists of accelerated atheroma, which is much more common and severe in diabetic patients. Microangiopathy is a distinctive feature of diabetes mellitus and particularly affects the retina, kidney and peripheral nerves. Diabetes mellitus is the commonest cause of chronic renal failure, which itself represents a huge and rapidly increasing problem, the costs of which to society as well as to individual patients are staggering. Coexistent hypertension promotes progressive renal damage nephropathy and reduces the risk of myocardial infarction. Angiotensin–converting enzyme inhibitors or antagonists of angiotensin AT_1 receptors are more effective in preventing diabetic nephropathy than other antihypertensive drugs, perhaps because they prevent fibroproliferative actions of angiotensin- II and aldosterone. Although the underlying mechanism of diabetic complications is unclear much attention has been focused on the role of oxidative stress, which contributes to the pathogenesis of different diabetic complications [8].

Traditional treatments for diabetes may create a feeling of improved well-being without necessarily reducing hyperglycemia. There have been unsubstantiated claims that certain plants can ameliorate complications of diabetes (Table 1), but the objective assessment of complications is difficult and the placebo effect of natural remedies cannot be discounted. No controlled studies of microvascular, macrovascular, or neuropathic complications have been undertaken with traditional therapies. A plant that is thirst quenching or increases sympathetic tone might gain a traditional reputation as efficacious without providing any long-term benefits to the underlying malady. Members of the *Allium* family, particularly garlic, are traditionally considered to give strength and combat arterial vascular disease [9]. Garlic reduces polydipsia and weight loss in severely streptozocin-induced diabetic mice without improving glycemic control [10]. Onion has been reported to lower free fatty acid concentrations in healthy subjects, and seeds of

T. foenumgraecum (fenugreek) reduced cholesterol levels in diabetic dogs [11,12]. Other traditional antidiabetic plants have been anecdotally claimed to possess hypolipidemic properties.

2.2 INSULIN THERAPY

Insulin is the mainstay for treatment of virtually type-1 DM and many type-2 diabetes mellitus patients. When necessary, insulin may be administered intravenously or intramuscularly; however, long-term treatment relies predominantly on subcutaneous injection of the hormone. Subcutaneous administration of insulin differs from physiological secretion of insulin in at least two major ways: The kinetics do not produce the normal rapid rise and decline of insulin secretion in response to ingestion of nutrients, and the insulin diffuses into the portal circulation; the direct action of secreted insulin on hepatic metabolic processes is thus eliminated.

3. SCREENING METHODS OF ANTIDIABETIC AGENTS [13,14]

Before the advent of insulin and oral hypoglycemic drugs, the major form of treatment involved the use of plants. More than 400 plants have been recommended and recent investigations have affirmed the potential value of some of these treatments. The hypoglycemic and/or anti-hyperglycemic effect of several plants used as anti-diabetic remedies have been confirmed and the mechanisms of their actions are being studied. Chemical studies directed at the isolation, purification and identification of the substances responsible for the anti diabetic activities are also being conducted various diabetogens.

Induction of experimental diabetes in the rat by particularly destroying the pancreatic beta cells is the most convenient method employed now a day and the most commonly used diabetogenic agents are alloxan and streptozotocin.

4. HERBAL DRUGS USED IN THE TREATMENT OF DIABETES

In the recent times many traditionally used medicinally important plants were tested for their anti-diabetic potential by various investigators in experimental animals. Several synthetic oral hypoglycemic agents that are used as conventional medicine today have a natural plant origin, eg: metformin was derived from the plant, *Galega officinalis* (Goat's Rue or French Lilae) which was a common remedy for diabetes [15,16]. The synthetic hypoglycemic agents used in clinical practices have serious side effects like hematological effects, coma, disturbs the functions of liver and kidney. In addition, they are not suitable for use during pregnancy. Compared with synthetic drugs, drugs derived from plants are frequently considered to be less toxic with fewer side effects. Therefore, the search for more effective and safer antidiabetic agent has become an area of active research. Most commonly used plants in herbal formulations in the treatment of diabetes are given in Table 2. The list of poly herbal formulation used is shown Table 3. The use of natural sweetener alternative to table sugar, artificial sweeteners like barley malt, maple syrup, rice syrup, fructose (fruit sugar) and the herb stevia are utilized more today. Stevia is an excellent natural alternative to artificial sweeteners. It is very concentrated, so only a small amount is used and it doesn't have the side effects that artificial sweeteners have. Aloe Vera, cinnamon, ginseng, onion, yam and ginseng powder are used as prediabetic remedy [17].

Table 1. Antidiabetic plants traditionally considered as efficacious in treatment of diabetes-associated complications

Complications	Plants
Polydipsia	*Panax ginseng, Polygonatum humile, Polygonatum macropodum, Polygonatum officinale.*
Emaciation	*Allium sativum, Cichorum intybus.*
Atherosclerosis	*Allium cepa, Allium sativum, Lycium chinensis, Panax ginseng, Taraxacum officinale, Trigonella foenumgraecum.*
Retinopathy	*Daucus carrota, Lycium chinensis, Taraxacum officinale, Vaccinium myrtillus*
Nephropathy	*Lycium chinensis.*
Impotence	*Ceiba petandra, Coriandrum sativum, Crocus sativa, Panax ginseng, Papaver somniferum.*

Table 2. Plants reported having antidiabetic activity

Plants	References
Abelmoschus moschatus Medik	[18]
Abrus precatorius L.	[19]
Acacia arabica	[19]
Achyranthes aspera L	[18]
Achyrocline satureioides	[20]
Acosmium panamense Schott.	[18]
Aegle Marmelos	[21]
Aerva lanata	[22]
Aegle marmelos	[23]
Agrimony eupatoria L.	[24]
Ajuga iva L. Schreberr	[18]
Allium cepa	[19,25]
Allium sativum	[19,26]
Alpinia galangal	[27]
Aloe vera and Aloe barbadensis	[19]
Andrographis paniculata Burm	[28]
Annona squamosa L	[29]
Aporosa lindleyana	[30]
Artemisia herba-alba Asso	[31]
Artemisia dracunculus L	[32]
Astragalus membranaceus Bunge	[18]
Averrhoa bilimbi	[33]
Azadirachta indica	[34]
Barleria lupulina	[35]
Bauhinia candicans	[36,37]
Bauhinia forficate Link	[18]
Berberis aristata	[38]
Bidens pilosa L	[39]
Biophytum sensitivum	[40]
Bixa orellana L	[41]
Boerhaavia diffusa	[42,43]
Boswellia glabra	[44]
Bougainvillea spectabillis	[45]
Brassica nigra (L) Koch	[46]
Bryonia alba L	[47]
Bumelia sartorum Mart	[48]
Caesalpinia bonducella	[49]
Cajanus cajan (L) Millsp	[50]
Carum carvi	[18]
Casearia esculenta Roxb	[51]
Cassia auriculata L	[52]
Catharanthus roseus	[53]
Chamaemelum nobile	[54]
Cichorium intybus L	[55]
Clausena anisata (Willd) Benth	[56]
Coriandrum sativum L	[57]
Combretum lanceolatum	[58]
Cuminum cyminum L	[59]
Curcuma longa	[60]
Cuminum nigrum L	[61]
Cyamopsis tetragonoloba (L) Taubert	[62]
Dioscorea dumetorum	[63]
Eclipta alba (L) Hassk	[64]
Emblica officinalis Gaertn	[65]

Plants	References
Enicostema littorale blume	[66]
Eugenia jambolina	[67]
Ficus bengalensis L	[68]
Fraxinus excelsior	[69]
Garcinia kola Heckel	[70]
Gongronema latifolium Endl	[71]
Gymnema Sylvestre	[72]
Helicteres isora L	[73,74]
Holostemma ada kodien	[75]
Hypoxis hemerocallidea conn Corm	[76]
Inula racemosa Hook	[18]
Lagerstroemia speciosa (L) Pers	[77]
Lepidium sativum L	[78]
Mangifera indica	[19]
Momordica charantia	[19,79,80]
Morinda lucida Benth	[18]
Myrcia uniflora Barb	[81]
Nigella sativa L	[82]
Ocimum gratissimum	[83]
Ocimum sanctum L	[84,85]
Origanum vulgare L	[86]
Otholobium pubescens L	[87]
Paeonia lactiflora Pall	[88]
Panax ginseng	[89]
Pterocarpus marsupium	[90]
Phyllanthus amarus Schum & Thonn	[91]
Psidium guajava L.	[92,93]
Pterocarpus marsupium Roxb	[94,95]
Retama raetam	[96,97]
Salacia reticulate W	[98]
Spergularia purpurea	[99]
Suaeda fruticosa (SF) Euras	[100]
Syzygium cumini	[101]
Talinum cuneifolium	[102]
Tamarindus indica L	[103]
Telfaria occidentalis Hook	[18]
Terminalia catappa	[104]
Terminalia chebula	[105]
Trigonella foenum graecum	[19]
Tinospora cordifolia	[19]
Urtica dioica	[106]
Vinca rosea	[107]
Zizypus jujube	[108]
Sphenocentrum jollyanum	[109]
Ocimum canum	[110]
Jatropha curcas	[111]
Lawsonia inermis	[112]
Ficus hispida	[113]
Pergularia daemia	[114]
Wattakaka volubilis	[19]

5. THE MECHANISM INVOLVED IN THE TREATMENT OF DIABETES

The present treatment of diabetes is focused on controlling and lowering blood glucose to a normal level. The mechanisms may be

- To stimulate cell of pancreatic islet to release insulin;
- To resist the hormones which rise blood glucose;
- To increase the number or rise the potency and sensitivity of insulin receptor sites to insulin;
- To decrease the leading-out of glycogen;
- To enhance the use of glucose in the tissue and organ;
- To clear away free radicals, resist lipid per oxidation and correct the metabolic disorder of lipid and protein;
- To improve microcirculation in the body.

Anti-diabetic medicinal plants undoubtedly have a significant effect on the lowering of blood sugar, but their mechanism of action is yet to be elucidated. The first evidence that the natural products have insulin potentiating activity was reported in 1929 by Glazer and Halpern. There are several mechanisms through which these herbs act to control the glucose level. They are more or less similar actions to the synthetic drugs. The mechanism of action of herbal anti-diabetics could be grouped as:

- Stimulation of insulin secretion (*Allium sativum* [26]*, Allium cepa* [25]*,*
- *Panax ginseng* [89]).
- Inhibition in renal glucose reabsorption (*Fraxinus excelsior* [69]).
- Stimulation of glycogenesis and hepatic glycolysis (*Momordica charantia* [80]).
- Protective effect on the destruction of the beta-cells (*Thea sinensis* [115]).
- Improvement of digestion and reduction of blood sugar and urea (*Aegle marmelos* [23]).
- Prevents pathological conversion of starch to glucose (*Eugenia jambolina* [67]*, Tinospora cordifolia* [67], *Pterocarpus marsupium* [90]).
- Increasing the use of glucose by tissues and effect on adrenergic receptors (*Panax Ginseng* [89]*, Allium sativum* [26]*, Allium cepa* [25]).
- Potentiates the action of exogenously injected insulin (*Nelumbo nucifera* [116]*, Rubia cordifolia* [117]).
- Cortisol lowering activities (*Boerhaavia diffusa* [42,43]*, Ocimum sanctum* [118]).

Table 3. Some of the Polyherbal formulations used in treatment of Diabetes mellitus

Formulation	Reference
Acanthopanax senticosus	[119]
Aavaraiyathi churnam	[120]
Alnus hirsuta	[119]
Ayushan- 82	[121]
Diabecon (D- 400)	[122]
Dianex	[123]
Diarun plus65	[124]
Rosa davurica	[119]
Panax schinseng	[119]
MA- 471	[125]

Over 150 plant extracts some of the active principles, including flavonoids are known to be used for the treatment of diabetes [126-128]. Huff and Howell reported that Quercetin stimulate insulin release and enhance calcium uptake from isolated cells, which suggest a place for flavonoids in NIDDM [129,130]. The presence of 3' and 4' –OH in the B-ring and double bonds between C_2 and C_3 in flavones and flavonols are important factors for binding enzyme glycogen phosphorylase [131] which is a key enzyme in the regulation of glycogen metabolism and catalyzes a degradative phosphorylysis of glycogen to glucose.

6. TOXIC EFFECTS OF HERBS

Little toxicological information exists concerning traditional antidiabetic plants. Use of the plants over many centuries and sometimes as regular constituents of the diet might be expected to reveal any obvious detrimental side effects through the cumulative knowledge of personal experiences. Nevertheless, patients are prone to overindulge in natural treatments, believing their efficacious reputation to imply safety, but chronic consumption of large amounts of traditional remedies must always be regarded with caution.

Catharanthus roseus (periwinkle) is widely used as a traditional treatment for NIDDM. Many major alkaloids isolated from this plant, including leurosine, vindoline, vindolinine, and catharanthine, recorded as mild hypoglycemic effect within 2-5 h in healthy rats, but none was sufficiently potent to encourage further investigation because of cytotoxic and neurological effects of *Catharanthus* alkaloids [132].

Ficus bengalensis (banyan tree), used traditionally in Asia for the treatment of DM, but studies on rats observed gross behavioral, neurologic, autonomic toxic effects [132]. A central nervous simulation and hypertensive effect of ephedrine from Ephedra species and central nervous stimulation by Panax species has limited their usage in the treatment of diabetes [89].

Unripe fruits of *Blighia sapida* (ackee fruit). A traditional treatment for diabetes in Central America and Africa. Hypoglycins (aminopropylpropionic acid derivatives) are effective in healthy and diabetic animals and humans, promoting glucose use and inhibiting gluconeogenesis secondary to the inhibition of long-chain fatty acid oxidation [133]. However, their toxic effects have precluded further development because it induces neuroglycopenia [134]. Other non-cultivated traditional antidiabetic mushrooms such as C. *comatus* can accumulate heavy metals with toxic consequences if consumed in excess. The poisonous effects of *A. phalloides* are probably due to neuroglycopenia after hepatic glycogen depletion and hepatic necrosis [135].

A study in South Africa recorded cases of spontaneous hypoglycemia, hepatic and renal necrosis after consumption of herbal medicines like *Adenia gummifera* (imfulwa), Chenopodium Ambrosioides*, Spilanthus Mauritania, Iboza riparia* [136]. A case-study report noted that the hypoglycemic effect of M. *charantia* was additive to that of chlorpropamide, and V. myrtillus*,* and synthalin apparently reduced insulin requirements [137-139].

7. CONCLUSION

This is an exciting time in medical and diabetic history. Diabetes is world's fast emergent metabolic disorder and a knowledge of this disorder increases, similar more appropriate therapies. Traditional plant medicines are used throughout the world for diabetes. So a study such medicine might offer a natural key to unlock a researcher in the future.

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It is not applicable.

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Author has declared that no competing interests exist.

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