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Review Article

Antidiabetic Potential of Herbal Plants

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ABSTRACT

Diabetes mellitus (DM), both insulin-dependent DM (IDDM) and non-insulin dependent DM (NIDDM) is a common and serious metabolic disorder throughout the world. Traditional plant treatments have been used throughout the world for the therapy of diabetes mellitus. Among many medications and polyherbal plants, several herbs have been known to cure and control diabetes; additionally they have no side effects. Diabetes mellitus is a dreadful disease found in all parts of the world and is becoming a serious threat to mankind health. Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion, or action, or both. Thus, plants are a potential source of anti-diabetic drugs which can be proved by the ethnobotanical information reports about 800 plants that may possess anti-diabetic potential. Although, synthetic oral hypoglycemic agents/insulin is the mainstream treatment of diabetes and effective in controlling hyperglycaemia, they have prominent side effects and fail to significantly alter the course of diabetic complications. This forms the main reason for an increasing number of people finding alternating therapies that may have less severe or no side effects. This article presents a review on some reported antidiabetic medicinal plants (with their botanical name, common name, constituent and mechanism of action for antidiabetic action) and plant based marketed polyherbal herbal formulations

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INTRODUCTION

Diabetes is a heterogeneous metabolic disorder characterized by altered carbohydrate, lipid and protein metabolism which causes hyperglycemia resulting from insufficient insulin secretion, insulin action or both.^{1,2} It is one of the refractory diseases identified by Indian council of medical research for which an alternative medicine is a need for the treatment. Diabetes mellitus has become a growing problem in the contemporary world.³ The biochemical parameters (glucose, urea, creatinine, serum cholesterol, serum triglyceride, high density lipoprotein, low density lipoprotein, hemoglobin and glycosylated hemoglobin) of the polyherbal formulation were assessed in diabetic. The product showed its effectiveness in oral glucose tolerance test but it does not produce hypoglycemic effect. Treatment of diabetic rats with the product restored the elevated biochemical parameters significantly. The present study supports the use of this product as an antidiabetic.⁴ The number of people with diabetes is increasing day by day the main cause of this problem is aging, urbanisation and increasing prevalence of obesity and physical inactivity. Quantifying the prevalence of diabetes and the number of

people affected by diabetes, now and in the future it is important to have rational planning and allocation of resources towards treatment and prevention of this disease. Diabetes is a metabolic disorder where in human body does not produce or properly uses insulin, a hormone that is required to convert sugar, starches, and other food into energy.⁵

Diabetes results in abnormal levels of glucose in the bloodstream. Herbal plants are very common in use in our day to day life. Either as a nutrient or as a source of food these herbs are being consumed by the patient as well as healthy person. Easy availability, raw consumption, least side effects and low cost makes the herbal preparations the king of all available therapies.⁶ The vast majority of cases of diabetes fall into two broad etiopathogenic categories. In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin-secretory response (American Diabetes Association, 2005). Currently available therapies for diabetes include insulin and various oral

antidiabetic agents such as sulfonylureas, biguanides and glinides.⁷ Many of them have a number of serious adverse effects; therefore, the search for more effective and safer hypoglycemic agents is one of the most important areas of investigation. In diabetes, hyperglycemia generates reactive oxygen species (ROS), which in turn cause lipid peroxidation and membrane damage and these free radicals play an important role in the production of secondary complications in diabetes mellitus (kidney, eye, blood vessel, and nerve damage).^{8,9} Antioxidants have been shown to prevent the destruction of β -cells by inhibiting the peroxidation chain reaction and thus they may provide protection against the development of diabetes.

Plants contain natural antioxidants (tannins, flavonoids, vitamins C and E, etc.) that can preserve β -cell function and prevent diabetes induced ROS formation. In this present review article an attempt was made to list out the herbal plants possessing antidiabetic activity by one or the other possible mechanisms.^{10,11} Diabetes mellitus is a serious health problem with continuously increasing rates of incidence and mortality. Diabetes mellitus is characterized by elevated plasma glucose concentrations resulting from insufficient insulin and insulin resistance, or both, leading to metabolic abnormalities in carbohydrates, lipids and proteins. If not cured or controlled it may even lead to acute or chronic complications causing ketoacidosis, microangiopathy and other related infections. Different types of reported diabetes mellitus can be classified under following two categories:

Type 1 is insulin-dependent diabetes mellitus (IDDM), in which the body does not produce any Insulin. It most often occurs in children and young adults. Type 1 diabetes accounts for 5–10% of Diabetes.

Type 2 is noninsulin-dependent diabetes mellitus (NIDDM), in which the body does not produce enough, or improper use of secreted insulin is the most common form of the disease, accounting for 90–95% of diabetes. Type 2 diabetes is nearing epidemic proportions, due to an increased number of elderly people, and a greater prevalence of obesity and sedentary lifestyles.

BASIS OF DIABETES MELLITUS TREATMENT:

- Patient education concerning the disease
- Physical exercise
- Diet and
- Hypoglycemic agents

As a very common chronic disease, diabetes is becoming the third “killer” of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases because of its high prevalence, morbidity and mortality. Therefore once diagnosed, it is well regulated by means of various therapeutically effective drugs. Besides, the therapy based on chemotherapeutic agents, the present century has progressed towards naturopathy. Thus, medical plants have an ever emerging role to play in treatment or management of lifelong prolonging diseases like diabetes mellitus, especially in developing countries where resources are meager. Diabetes mellitus alone is accompanied with several other diseases infecting healthy individuals. The treatment of each of such disease can be done by exploiting the herbal integrity of India. The plants in parts or as full can be used for curing any disorder related with diabetes mellitus. Moreover, in some cases extracts of plants are self-capable of treating the related disorders such as polyuria, polydipsia,

glucosuria, etc. along with curing the chronic disorders such as diabetes mellitus.

Advantages^{14,15}

- Mostly herbal drugs are well tolerated by the patient, having fewer unintended consequences and fewer side effects than traditional medicine, and may be safer to use.
- Herbal drugs are more effective for long-standing health complaints that don't respond well to traditional medicine
- Cost of herbal drugs is much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.
- Herbs are available without a prescription. Simple herbs, such as peppermint and chamomile, can be cultivated at home.

Life style for patient^{16, 17}

- Some of the home and herbal remedies prescribed by Ayurveda are described below.
1. Include turmeric and cinnamon diets.
 2. Avoid oily, fried and starchy foodstuffs.
 3. Avoid coffee, sugar, refined flour and alcohol.
 4. Eat smaller meals (low fat diet) five to six times a day instead of having three large meals.
 5. Increase intake of vegetables like spinach, cucumber, tomatoes, onion, sprouts, beans, garlic etc.
 6. Refrain from taking stress.
 7. Regular exercise. Walk for at least 40 minutes a day.
 8. Avoid red meat and excessive salt in your meals. Fish and soy can be taken due to their good protein value.
 9. Avoid white bread, rice, potatoes, sweet and sugary foods.

Recent Regulatory Developments:

Herbal drugs, as defined by regulatory measures constitute only those traditional medicines, which primarily use medicinal plant preparations for therapy. WHO has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, almost for several hundreds of years, before the development and spread of modern medicine and others which are still in use. In recent years FDA and EMEA have taken keen interest and also have reviewed the regulatory frameworks governing the development and use of botanical drugs. This keen interest has provided a significant fillip to the natural products industry and has significantly lowered the entry barriers for botanicals and related products. These new guidelines more importantly also provide guarantees of market exclusivity for botanicals as well as the acceptance of synergistic combinations of plant derived bioactive products. Developing and developed countries such as India and China have clearly a natural advantage over the others.^{18,19}

MECHANISM OF ACTION OF HERBAL ANTIDIABETICS^{20, 21}

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanism of action of herbal antidiabetic could be grouped as:

- Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2nd messenger) stimulation
- Inhibition in renal glucose reabsorption
- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes
- Reduction in insulin resistance
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells
- Regenerating and/or repairing pancreatic beta cells
 - Increasing the size and number of cells in the islets of Langerhans
- Stimulation of insulin secretion
- Stimulation of glycogenesis and hepatic glycolysis
- Protective effect on the destruction of the beta cells
- Improvement in digestion along with reduction in blood sugar and urea
- Prevention of pathological conversion of starch to glucose
- Inhibition of β -galactosidase and α -glucosidase
- Cortisol lowering activities
- Inhibition of alpha-amylase

MEDICINAL PLANTS WITH ANTIDIABETIC AND RELATED BENEFICIAL PROPERTIES

Acacia arabica (Mimosaceae)

It occurs in wild throughout India and is also cultivated. Feeding of 94% seed diet to normal rats showed significant hypoglycemic effect versus controls. However, the same diet failed to show any hypoglycemic effect in alloxanized rats (175 mg/kg SC) indicating that plant acts through release of insulin. Powdered seeds of Acacia Arabica administered in doses of 2, 3 and 4 gm/kg body weight exerted a significant

(PB/0.05) hypoglycemic effect in normal rabbits by initiating the release of insulin from pancreatic beta cells. No acute toxicity and behavioural changes were observed at these doses. It is found all over India. The plant extract acts as an antidiabetic agent by acting as secretagogue to release insulin. It induces hypoglycemia in control rats but not in alloxanized animals. Powdered seeds of *A. arabica* when administered (2, 3 and 4 g/kg body weight) to normal rabbits, induces hypoglycemic effect by initiating release of insulin from pancreatic beta cells.^{22, 23}

Achyranthes aspera (Amaranthaceae)

It is distributed throughout the tropical world. Oral administration of *A. aspera* powder produces a significant dose-related hypoglycemic effect in normal as well as in diabetic rabbits. The water and methanol extracts also decreases blood glucose levels in normal and alloxan diabetic rabbits. The acute toxicity study in rabbits does not reveal any adverse or side effects of this folk medicine at dosages up to 8 g/kg orally. The plant could act by providing certain necessary elements like calcium, zinc, magnesium, manganese and copper to the beta-cells.^{23, 24}

Allium cepa, onion (Liliaceae)

Allium cepa is known only in cultivation but related wild species occur in Central Asia. Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits.^{25, 26} *A. cepa* also known to have antioxidant and hypolipidemic activity. Administration of a sulfur containing amino acid, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues. It normalizes the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase.^{27, 28} When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels.^{29, 30}



Fig1: Acacia arabica



Fig2: allium cepa

Allium sativum, garlic (Liliaceae)

It is a perennial herb cultivated throughout India and is commonly used as a food ingredient. Oral administration of 0.25 gm/kg of ethanol, petroleum ether, ethyl ether extract of *Allium sativum* causes 18.9, 17.9, 26.2% reduction in blood sugar in alloxan diabetic rabbits (150 mg/kg IV). Oral administration of 0.25 gm/kg allicin (isolated from *A. sativum*) produced hypoglycemia comparable to tolbutamide in mildly diabetic rabbits (glucose levels ranging from 180 to 300 mg %), while it showed no such effect in severely diabetic animals (blood sugar >350 mg %). Aqueous

homogenate of garlic (10 ml/kg/day) administered orally to sucrose fed rabbits (10 gm/kg/day in water for 2 months) significantly increased hepatic glycogen and free amino acid contents, decreased fasting blood sugar, triglyceride levels in serum, liver and aorta and protein levels in serum and liver in comparison to sucrose controls. Oral administration of the garlic extract significantly decreases serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST and ALT levels, while increases serum insulin in diabetic rats but not in normal rats when compared with antidiabetic drug glibenclamide. The antidiabetic effect of the extract was more effective than glibenclamide. It is concluded that the

plant must be considered as excellent candidate for future studies on diabetes mellitus.^{31, 32}

***Aloe barbadensis*, *Aloe gibberellins* (Liliaceae)**

It grows in arid climates and is widely distributed in Africa, India and other arid areas. Aloe vera gel at 200 mg/kg had significant antidiabetic and cardioprotective activity and reduces the increased TBARS and maintains the Superoxide dismutase and Catalase activity up to the normal level and increases reduced glutathione by four times in diabetic rats.³³ The leaf pulp extract showed hypoglycemic activity on IDDM and NIDDM rats, the effectiveness being enhanced for type II diabetes in comparison with glibenclamide. Both Aloe vera and (over a dose range of 2-100 mg/kg) inhibit inflammation in a doseresponse manner and improve wound healing in STZ diabetic mice. The dried sap of the plant (half a teaspoonful daily for 4-14 weeks) has shown significant hypoglycemic effect both clinically as well as experimental³⁴

***Aloe vera* (Liliaceae)**

It is a cactus like plant with green dagger shaped leaves that are fleshy tapering, spiny and filled with clearly viscous gel.

The aqueous extract of Aloe vera has the hypoglycemic property which was given orally at a dose of 150mg/kg of body weight. Whole study was performed on the alloxan induced male albino rats, Treatment of chronic but no single dose of exudates of Aloe barbadensis leaves shows hypoglycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also show hypoglycaemic effect in diabetic rats. This action is through stimulation of synthesis and/or release of insulin from pancreatic beta cell.^{35, 36}

***Andrographis paniculata* (Acanthaceae)**

It is a herbaceous plant native to India, Sri Lanka and widely cultivated in southern Asia. Oral administration of andrographis significantly increases the activity of SOD and Catalase. Also decreases blood glucose levels due to its antioxidant properties. The ethanolic extract of A. paniculata possesses antidiabetic property and may be attributed at least in part to increase glucose metabolism. Its hypotriglyceridemic effect is also beneficial in the diabetic state.^{37,38}



Fig3: *Allium sativum*



Fig4: *Aloe vera*



Fig5: *Andrographis paniculata*

***Annona squamosa* (Annonaceae)**

It is a small well-branched tree or shrub, grows at lower altitudes. Administration of 15 mg/kg/day of isolated juercetin-3-O-glucoside from Annona squamosa leaves for 10 consecutive days to the hyperglycemic animals reverse these effects and simultaneously inhibits the activity of hepatic Glucose-6-phosphatase. Aqueous extract of A. squamosa root (at a dose of 250 mg/kg and 500 mg/kg bw) when given to STZ- induced diabetic rats reduced the blood glucose level from 285.52 to 208.81 mg/dl, 6 hours after oral administration of extract. It further decreases the hepatic and renal lipid peroxidation with a concomitant increase in the activities of antioxidative enzymes, such as Catalase and Superoxide dismutase as well as glutathione content, indicating its safe and antiperoxidative effects.^{39, 40}

***Azadirachta-indica* (Meliaceae)**

Commonly known as Neem. It is a tree native to India, Burma, Bangladesh, Sri Lanka, Malaysia and Pakistan, growing in tropical and semi-tropical regions. A low (0.5g tid) and high (2g tid) doses of powdered part, aqueous extract and alcoholic extract of A. indica shows significant hypoglycemic activity in high dose and can be successfully combined with oral hypoglycemic agents in type-2 diabetic patients whose diabetes is not controlled by these agents.⁴¹

***Catharanthus roseus* (Apocynaceae)**

Oral administration at dose-dependent of 0.5, 0.75 and 1.0 mL/kg body weight reduced the blood glucose of both normal and diabetic rabbits comparable with that of the standard drug, glibenclamide. The results indicate a prolonged action in reduction of blood glucose by C. Roseus and the mode of action of the active compound(s) is probably mediated through enhance secretion of insulin from the betacells of Langerhans or through extra pancreatic mechanism.⁴⁴

Fig6: *Azadirachta indica*Fig7: *Catharanthus roseus****Momordica charantia* L. (Cucurbitaceae)**

M. charantia (bitter melon) is commonly known as vegetable insulin. An oral sucrose tolerance test reveals that administration of aqueous extract (AE), methanol fraction (MF) or methanol insoluble fraction (MIF) each significantly suppresses plasma glucose levels at 30 min as compared with control. In addition, the plasma insulin level at 30 min also lowers after MF administration than the control in the oral sucrose tolerance test, these results demonstrates that bitter melon suppresses postprandial hyperglycemia by inhibition of α glucosidase activity.⁴⁵

***Panax ginseng* (Araliaceae)**

The roots are taken orally in the treatment of type II diabetes. Extracts of ginseng species shows antihyperglycemic activity associated with increased peroxisome proliferatoractivated receptor gamma expression and adenosine monophosphate-activated protein kinase phosphorylation in liver and muscle. Oral administration of *P. ginseng* root improves insulin sensitivity and may be used as an adjuvant therapy for treating diabetic patients with insulin resistance.^{46, 47, 48,}

***Ocimum sanctum* L. (Lamiaceae)**

It is commonly known as Tulsi. Since ancient times, this plant is known for its medicinal properties.^{49,50} The aqueous extract of leaves shows significant reduction in blood sugar level in both normal and alloxan induced diabetic rats .Significant reduction in fasting blood glucose, uronic acid,

total amino acid, total cholesterol, triglyceride and total lipid indicate the hypoglycemic and hypolipidemic effects of tulsi in diabetic rats.^{51, 52} Oral administration of plant extract (200 mg/kg) for 30 days leads to decrease in the plasma glucose level. Renal glycogen content increases 10 fold while skeletal muscle and hepatic glycogen levels decreases by 68% and 75% respectively in diabetic rats as compared to control. This plant also shows antioxidant, antibacterial, antifungal, antiviral, antiasthmatic, antistress, antitumor, gastric antiulcer activity, antimutagenic and immunostimulant activities.^{53, 54}

***Mangifera indica* (Anacardiaceae)**

The aqueous extract produces reduction of blood glucose level in normoglycemic and glucose-induced hyperglycemia, but does not have any effect on streptozotocin-induced diabetic mice under the same conditions when compared with that of an oral dose of chlorpropamide. The result indicates that the aqueous extract of the leaves of *M. indica* possess hypoglycemic activity.^{53, 54}

***Tinospora cordifolia* (Menispermaceae)**

Commonly known as Guduchi, an herbaceous vine indigenous to the tropical areas of India, Myanmar and Sri Lanka. Oral administration of an aqueous *T. cordifolia* root extract to alloxan diabetic rats causes a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg/kg could elicit significant antihyperglycemic effect in different animal models, its effect is equivalent to only one unit/kg of insulin.^{55, 56}

Fig8: *Tinospora cordifolia*Fig9: *Ocimum sanctum*

Table 1: Some Plants Having Hypoglycemic Activities.⁷⁷

S.no.	Common name	Botanical name and family	Parts used	Therapeutic action
1	Asiatic ginseng	Panax ginseng (Araliac)	Roots	Lowers blood glucose by decreasing the rate of carbohydrate absorption, increasing glucose transport and modulation of insulin secretion
2	Ashwagandha, winter cheery	Withania somnifera (Solanaceae)	Roots	Decrease in blood sugar level
3	Asiatic sweet leaf	Symplocos Paniculata (Symplocaceae)	Leaves/ stems	Inhibit protein tyrosine phosphatase 1B (PTP1B) 1 and 2
4	Banana	Musa sapientum Kuntz (Musaceae)	Fruits/flowers	Decreases blood glucose and glycosylated haemoglobin level
5	Banyan tree	Ficus bengalensis (Moraceae)	Bark	Inhibits insulinase activity from liver and kidney, stimulates insulin secretion
6	Barbados	Aloe barbadensis Mill. (Liliaceae)	Leaves	Stimulate synthesis and release of insulin
7	Betal, betal wine	Piper betle (Piperaceae)	Leaf	Antihyperglycemic, glucose metabolism
8	Bilwa, bael fruit	Aegle marmelos (Rutaceae)	Leaf Extract	Decrease blood urea and cholesterol
9	Bitter kola, false kola	Garcinia kola (Clusiaceae)	Seed	Hypoglycaemic and Hypolipidemic
10	Black tea	Camellia sinensis L. (Theaceae)	Leaves	L. (Theaceae) Leaves Decreases blood glucose level

Table 2: Marketed Herbal Antidiabetic Products

S.no.	Product	Manufacturer	Mechanism	Reference
1	Sharang Dyab-Tea	Plant Med lab Pvt. Ltd.	Stimulate insulin production	[81]
2	Herbal hills jambu	Isha Agro Developers	Reduce blood and urine sugar level	[82]
3	Stevia-33	Vitalize Herbs Pvt. Ltd.	Stimulate beta cells of pancreas	[83]
4	Diab-FIT	Herbal FIT	Maintain proper blood sugar level	[84]
5	Madhumar capsule	Kangrd Hills Care and Products	Control chronic care diabetes mellitus	[85]
6	Daya Stone Powder	Jignesh and Co.	Lower the blood glucose level	[86]
7	Blue berry Al	Hikma FZCO	Antidiabetic	[87]
8	Episulin	Varuna Biocell Pvt. Ltd.	Antidiabetic	[88]



Fig 10: Stevia 33

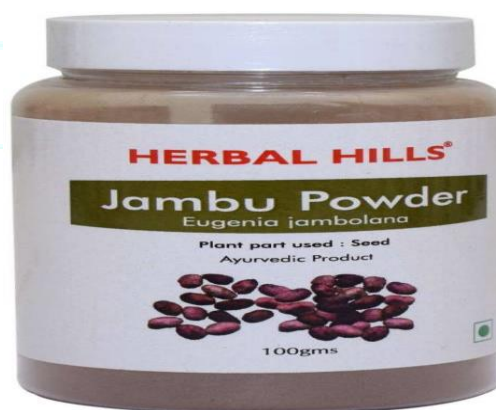


Fig 11: Herbal hills jambu powder

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CONCLUSION

Diabetes mellitus is the most common endocrine disorder, affecting more than 300 million people worldwide. For this, therapies developed along the principles of western

medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects and are often too costly, especially for the developing world. The prevalence of diabetes mellitus continues to rise worldwide and treatment with oral hypoglycemic drugs ends with numerous side effects and huge monetary expenditure. There is increasing demand by patients to use the natural products with antidiabetic activity. This paper has presented various anti-diabetic plants that have been pharmacologically tested and shown to be of some value in treatment of Diabetes Mellitus. The effects of these plants may delay the development of diabetic

complications and correct the metabolic abnormalities. However, more investigations must be carried out to evaluate the mechanism of action of medicinal plants with antidiabetic effect

The aim of present review is to establish the use of plants, plant parts or extract in curing Diabetes mellitus. It also collates available data on plants with hypoglycemic effects. In the present investigation, interest is focused on experimental studies performed on hypoglycemic Plants and their bioactive components. A brief description is given about the, type of diabetes, related physiological disorders and available herbal plants which can be further exploited for antidiabetic activity. Overall, this review presents the profiles of plants with hypoglycaemic properties, reported in the literature. All the herbal drugs discussed.

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