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HERBAL MEDICINES USED IN THE THERAPY OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is caused due to deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. It is a global problem and number of those affected is increasing day by day. The plants provide a potential source of hypoglycaemic drugs because many plants and plant derived compounds have been used in the treatment of diabetes. Several medicinal plants have found potential use as hypoglycaemic in the Indian system of medicines, including ayurveda. Many Indian plants have been investigated for their beneficial use in different types of diabetes. The use of herbs as hypoglycaemic is a major avenue in Indian perspectives particularly for treating diabetes, which require to be explored more effectively. Ayurveda and other Indian literature advocate the use of medicinal plants in treatment of various human diseases.

INTRODUCTION¹

Definition of Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion, or its action, or both. Diabetes mellitus, commonly referred to as diabetes (as it will be in this article) was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycaemia) lead to spillage of glucose into the urine, hence the term sweet urine. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates (for example, after eating food), insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia. Diabetes is a medical condition, meaning that although it can be controlled, it lasts a lifetime.

Classification^{2, 3}

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes and "other specific types". The "other specific types" are a collection of a few dozen individual causes. The term "diabetes", without qualification, usually refers to diabetes mellitus. The rare disease diabetes insipidus has similar symptoms as diabetes mellitus, but without disturbances in the sugar metabolism (*insipidus* means "without taste" in Latin). The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and noninsulin-dependent diabetes mellitus (NIDDM). Beyond two types, there is no agreed-upon standard nomenclature.

Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe to dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used. There are many reasons for type 1 diabetes to be accompanied by irregular and unpredictable hyperglycemias, frequently with ketosis, and sometimes serious hypoglycemias, including an impaired counterregulatory response to hypoglycemia, occult infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's disease). These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.

Type 2 diabetes

Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type. In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycaemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life. Hyperbilirubinemia may result from red blood cell destruction. Labour induction may be indicated with decreased placental function. A Caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia. A 2008 study completed in the U.S. found the number of American women entering pregnancy with pre-existing diabetes is increasing. In fact, the rate of diabetes in expectant mothers has more than doubled in the past six years. This is particularly problematic as diabetes raises the risk of complications during pregnancy, as well as increasing the potential for the children of diabetic mothers to become diabetic in the future.

Other types

Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes which has been termed "America's largest healthcare epidemic. Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology. Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, *malnutrition-related diabetes mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by World Health Organization when current taxonomy was introduced in 1999.

Causes ⁴

The cause of diabetes depends on the type.

Type 1 diabetes is partly inherited, and then triggered by certain infections, with some evidence pointing at Coxsackie B4 virus. A genetic element in individual susceptibility to some of these triggers has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 DM seems to require an environmental trigger. The onset of type 1 diabetes is unrelated to lifestyle.

Type 2 diabetes is due primarily to lifestyle factors and genetics.

The following is a comprehensive list of other causes of diabetes:

1. Genetic defects of β -cell function
 - a. Maturity onset diabetes of the young
 - b. Mitochondrial DNA mutations
2. Genetic defects in insulin processing or insulin action

- a. Defects in proinsulin conversion
 - b. Insulin gene mutations
 - c. Insulin receptor mutations
3. Exocrine pancreatic defects
 - a. Chronic pancreatitis
 - b. Pancreatectomy
 - c. Pancreatic neoplasia
 - d. Cystic fibrosis
 - e. Hemochromatosis
 - f. Fibrocalculous pancreatopathy
4. Endocrinopathies
 - a. Growth hormone excess (acromegaly)
 - b. Cushing syndrome
 - c. Hyperthyroidism
 - d. Pheochromocytoma
 - e. Glucagonoma
5. Infections
 - a. Cytomegalovirus infection

Symptoms⁵

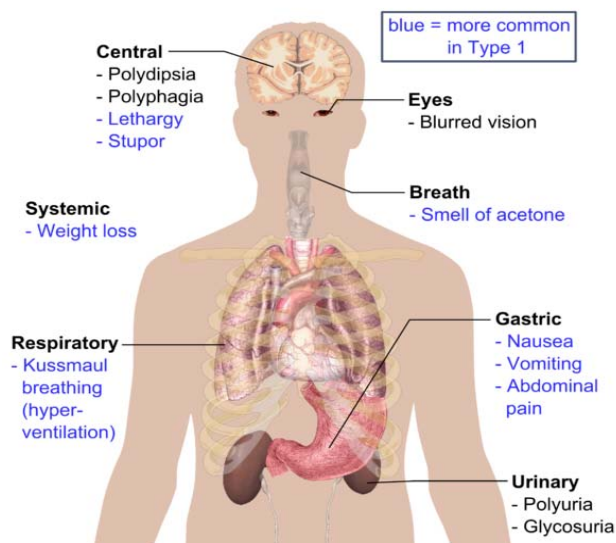


Fig no.1: Main symptoms of diabetes

- The early symptoms of untreated diabetes are related to elevated blood sugar levels, and loss of glucose in the urine. High amounts of glucose in the urine can cause increased urine output and lead to dehydration. Dehydration causes increased thirst and water consumption.
- The inability of insulin to perform normally has effects on protein, fat and carbohydrate metabolism. Insulin is an anabolic hormone, that is, one that encourages storage of fat and protein.
- A relative or absolute insulin deficiency eventually leads to weight loss despite an increase in appetite.
- Some untreated diabetes patients also complain of fatigue, nausea and vomiting.
- Patients with diabetes are prone to developing infections of the bladder, skin, and vaginal areas.
- Fluctuations in blood glucose levels can lead to blurred vision. Extremely elevated glucose levels can lead to lethargy and coma.

Diagnosis^{6,7}

Diabetes diagnostic criteria			
Condition	2 hour glucose	Fasting glucose	HbA _{1c}
	mmol/l(mg/dl)	mmol/l(mg/dl)	%
Normal	<7.8 (<140)	<6.1 (<110)	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥110) & <7.0(<126)	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥6.5

Diabetes mellitus is characterized by recurrent or persistent hyperglycaemia, and is diagnosed by demonstrating any one of the following:

Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)

Plasma glucose ≥ 11.1 mmol/l (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test

Symptoms of hyperglycaemia and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

Glycated hemoglobin (Hb A1C) $\geq 6.5\%$. A positive result, in the absence of unequivocal hyperglycaemia, should be confirmed by a repeat of any of the above methods on a different day.

It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) is considered diagnostic for diabetes mellitus. People with fasting glucose levels from 110 to 125 mg/dl (6.1 to 6.9 mmol/l) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two prediabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as cardiovascular disease. Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.

Important medicinal plants having antidiabetic potential:¹³

Importance of herbal medicines

Herbalists treat many conditions such as asthma, eczema, premenstrual syndrome, rheumatoid arthritis, migraine, menopausal symptoms, chronic fatigue, and irritable bowel syndrome, among others. Herbal preparations are best taken under the guidance of a trained professional. Be sure to consult with your doctor or an herbalist before self-treating. Some common herbs and their uses are discussed below.

ANTIDIABETIC PLANTS^{8,9}

Ayurveda and other Indian literature advocate the use of medicinal plants in treatment of various human diseases. India has about 45,000 plant species and among them, several thousands have been claimed to possess medicinal properties. Researchers conducted in the last few decades on plants, mentioned in ancient literature or used traditionally for diabetes, have shown antidiabetic property. Among them, 30 plants and their products (active natural principles and crude extracts) that have been mentioned used in the Indian traditional system of medicine have shown experimental or clinical antidiabetic activity. *Trigonella foenumgraecum*, *Momordica charantia*, *Tinospora cordifolia*, *Enicostema littorae*, *Gymnema sylvestre*, *Azadirachta indica*, *Syzygium cumini* are some of the most effective and the most commonly studied Indian plants in relation to diabetes.

Bauhinia forficata:

Family: Caesalpiniaceae

Bauhinia forficata is the most widely used herbal medicine for control of diabetes in Brazil, where it is known as Pata de Vaca. The fresh leaves are the essential part of this plant which shows the hypoglycaemic activity and the genus *Bauhinia* belongs to the family *Caesalpinaceae*. The initial reports of *Bauhinia forficata* antidiabetic activity in diabetic patients were made by Juliani (1941) and Juliani (1931). According to M.T. Pepato et al (2002) *Bauhinia forficata* decoction was prepared by boiling 150 g of fresh leaves in 1 litre of water for 5 min, allowed the decoction to stand for 30 min and filtered. The rats which are used for the experiment were fed a normal laboratory chow diet containing (wt./wt.) 16% protein, 66% carbohydrate and 8% fat and were housed under a 12:12 h light: dark cycle at 22-25°C. In this experiment they divided the rats into two groups i.e., diabetic and non diabetic groups, followed by administered the streptozotocin (STZ) 40 mg/kg body weight, after 3 days the serum and urinary glucose levels were increased. Then one group was injected with *Bauhinia forficata* decoction and another with the drinking-water as control group. After 31 days of treatment the diabetic group treated with decoction showed a significant reduction in plasma glucose and urinary glucose. So the pharmacological, biochemical, histological and chemical studies are needed to elucidate the exact mechanism of action of *Bauhinia forficata* leaf decoction and to isolate any active compounds. Such investigations should also be carried out regarding type 2 diabetes.

Ricinus communis

Family: Euphorbiaceae

Ricinus communis is the traditional medicine which was used for the management of Diabetes mellitus. It is called as Erandah in Sanskrit, Amudam in Telugu and Arandi in Hindi and is also known as castor oil. It belongs to the family *Euphorbiaceae*, and it was cultivated all over India for getting its seed oil. Castor oil have been used in classical Egyptian and Greek medicine and their use has been described in the *Susruta* and *Ayurveda* as early as sixth century B.C. In the Indian system of medicine, the leaf, root and seed oil of this plant have been used for the treatment of information and liver disorders. Fifty percent of ethanolic extract of the root, stem and leaves of this plant showed hypoglycaemic activity in normal animals and antihyperglycemic activity in diabetic animals in initial screening studies. The Administration of the ethanolic extract for a long duration led to a significant.

Panax ginseng

Family: Araliaceae

Ginseng polypeptide, isolated from the root of *Panax ginseng*, was demonstrated to decrease the level of blood sugar and liver glycogen when injected intravenously to rats. Mice were injected subcutaneous daily dose of 50 and 100 mg/kg for 7 successive days. GPP was also found to decrease blood glucose and liver glycogen and various experimental hyperglycaemia induced by injection of adrenaline glucose and alloxan. The aqueous extract of root of *panax ginseng* showed a remarkable hypoglycaemic activity on administration to mice. The hypoglycaemic effect of *pongamia pinnata* flowers, in normal persons and outdoor patients suffering from non-insulin dependent diabetes mellitus (NIDDM).

Allium sativum

Common name: garlic

Family: Alliaceae

Srivastava K, et.al suggested that the extract of *A. sativum* inhibits the formation of diabetic cataract due to excessive accumulation of polyols and hydration of the lenses of diabetic rats fed with galactose-, glucose and xyloserich diet. 5- Methyl cysteine sulphoxide, a sulphur containing amino acid isolated from *A. cepa*, showed antidiabetic effect on oral administration of the compound at dose 200 mg/kg for a period of 45days to alloxan diabetic rats. Kumar V, et.al suggested that it controlled the blood glucose in serum and altered the activities of liver hexokinase glucose-6-phosphatase and haemoglobin coenzyme-A reductase towards normal. Administration of aqueous extract of *Allium sativum* (garlic) in the concentration of 10 ml/kg/day to rabbits significantly increased liver glycogen and free amino acids, which resulted in significant decrease in fasting blood sugar, triglycerides (in serum, liver and aorta) and liver serum proteins as compared to those in sucrose-fed group.

Ocimum sanctum(Tulsi)

Family: Labiatae

Oral administration of an alcoholic extract of leaves of *Ocimum sanctum* Linn. (Tulasi) reduced glycaemia in normoglycaemic, glucose-fed hyperglycaemic and streptozotocin-induced diabetic rats. Furthermore, the extract potentiated the action of exogenous insulin in healthy rats. The activity of the extract was 91% and 70 % that of tolbutamide in healthy and diabetic rats, respectively. Reduction in fasting blood glucose was obtained after one month of treatment of healthy and diabetic rats with *O. sanctum* leaf powder.

Allium cepa L.

Family: Liliaceae

Common name: onion

Allium cepa (onion) was investigated for its hypoglycaemic activity by Collip and Janet, Laurin Brahmachari and Augusti reported that the petroleum ether extract of dried onion has hypoglycaemic activity and suggested that it can be a useful substitute for tolbutamide in controlling alloxan diabetes in rats.

Aloes vera:

Common name: Aloe

Family: Aloaceae

Ghannam et al. carried out their study on 5 patients with NIDDM and also on alloxan treated diabetic mice. They reported that oral administration of aloes lowers the fasting serum glucose levels in normal and diabetic subjects.

Azadirachta indica

Common Name: Limdo(Guj), Neem(Hindi).

Family: Meliaceae

Parts used: Whole plants.

Effect of *Azadirachta indica* leaf extract on serotonin inhibition in glucose-mediated insulin release in rat pancreas was reported to elucidate the possible mechanism of antihyperglycemic effect. *A. indica* leaf extract blocks significantly the inhibitory effect of serotonin on insulin secretion mediated by glucose. Hypoglycaemic effect observed with *Azadirachta indica* when given as leaf extract and seed oil was comparable to that of glibenclamide. *A. indica* could be of benefit in diabetes mellitus for controlling the blood sugar or may also be helpful in preventing or delaying the onset of the disease.

Acacia arabica :

Common name: Indian Gum Arabic tree

Family: Leguminosae

Acacia arabica (Lam.) Muhl. ex Willd. is a moderate sized, almost evergreen tree found throughout the drier parts of India, ascending to an altitude of 900 m. The bark of this plant has various traditional uses. It has also been reported for significant hypoglycaemic activity.

Pterocarpus marsupium**Family** : Fabaceae

The decoction of *P. marsupium* was administered for diabetes mellitus patients for 30 days. Singh, AK et al. revealed that the decoction is effective in the management of diabetes mellitus. Feeding the ethyl acetate soluble fraction of an absolute ethanol extract of *P. marsupium* wood for 5 days to alloxan diabetic rats significantly lowered blood sugar level (Ahmad, 1991). (Chakrabarti D et al. suggested that aqueous extract of *P. marsupium* exhibited antidiabetic activity in diabetic rats and human beings. The blood sugar lowering effect of 95% ethanolic extract of Red Sandal hyperglycaemic and streptozotocin diabetic albino rats. It was found to be effective in lowering the glucose level (Nagaarjun 1991). Epicatechin, isolated from the heartwood of *Pterocarpus marsupium*, showed regeneration of the b-cell population of the islets, which were earlier necrotic by alloxan.

Tinospora cordifolia¹⁰ (Gaduchi)**Family**: Menispermaceae.

Tinospora cordifolia have insulin-like action and can significantly reduce the blood glucose but not the lipid levels in alloxan induced rabbits. Literature supports the traditional belief that *T. crispa* extract effects in the treatment of diabetes by its action on the endocrine pancreas. Oral administration of the extract of *Tinospora cordifolia* roots for 6 weeks resulted in significant reduction in blood-urine glucose and in lipids in serum and showed its hypoglycaemic action.

T. crispa**Family**: Menispermaceae

The mechanism of action of antihyperglycemic effect of *T. crispa* is not due to interference with intestinal glucose uptake or uptake of the sugar into the peripheral cells. The antihyperglycemic effect of *T. crispa* is probably due to stimulation of insulin release via modulation of β -cells. That the insulinotropic effect of *T. crispa* is physiological suggests that the extract contains a compound that could be purified for use in the treatment of type-2 diabetes.

Andrographis paniculata Nees¹¹ (Kalmegh)**Family**: Rutaceae**Common name**: Kalmegh

Parts used: Whole plant

It is an erect annual herb commonly known as Kalmegh or 'King of Bitters', found throughout India and cultivated in many states of India. A number of studies have shown that *Andrographis paniculata* extract and the active metabolite andrographolide can exert potent antihyperglycemic activity.

Beta vulgarise L.

Common name: Garden beet

Family: Chenopodiaceae

Commonly known as garden beet is used traditionally in the management of diabetes in different parts of India. Various glycosides (Beta vulgarosides I–IV) isolated from the root of this plant were investigated for hypoglycaemic activity. The extract of the plant was also found to be effective in inhibiting non-enzymatic glycolization of skin proteins in streptozotocin-induced diabetic rats.

Coccinia indica .¹²

Family: Cucurbitaceae.

Parts used: Leaves

A creeper grows wildly in many parts of the Indian sub-continent and is well known as an hypoglycaemic herb. The hypoglycaemic activity of the plant was reported by Khan et al. (1980). Hypoglycaemic activity of Pectin, isolated from the fruit of *Coccinia indica* was studied in normal rats at a dose of 200 mg/100 g/day upon oral administration and it showed significant reduction in blood glucose and an increase in the liver glycogen level (Kumar et al., 1993). Ethanolic leaf extract of *Coccinia indica* (200 mg/kg for 45 days) also produced a modulatory effect on the aortic collagen content of STZ diabetic rats by reducing the accumulation and cross-linking of collagen (Venkateswaran et al., 2003). The extract also exhibited significant antioxidant activity (Venkateswaran and Pari, 2003a and Venkateswaran and Pari, 2003b) and hypolipidaemic activity (Pari and Venkateswaran, 2003) in streptozotocin induced diabetic rats.

Eugenia jambolana: (Indian gooseberry, jamun)

Family Name: Myrtaceae

Botanical Name: Syzygium Cumini

In India decoction of kernels of *Eugenia jambolana* is used as household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Antihyperglycemic effect of aqueous and alcoholic extract as well as lyophilized powder shows reduction in blood

glucose level. This varies with different level of diabetes. In mild diabetes (plasma sugar >180 mg/dl) it shows 73.51% reduction, whereas in moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl) it is reduced to 55.62% and 17.72% respectively. The oral administration of the extract resulted in increase in serum insulin levels in diabetic rats. Insulin secretion was found to be stimulated on incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic animals.

CONCLUSION

Diabetes is a disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or mounting resistance to its action. Herbal treatments for diabetes have been used in patients with insulin-dependent and non-insulin-dependant diabetes, diabetic retinopathy, diabetic peripheral neuropathy, etc. Scientific validation of several Indian plant species has proved the efficacy of the botanicals in reducing the sugar level. From the reports on their potential effectiveness against diabetes, it is assumed that the botanicals have a major role to play in the management of diabetes, which needs further exploration for necessary development of drugs and nutraceuticals from natural resources. However many herbal remedies used today have not undergone careful scientific assessment and some have the potential to cause serious toxic effects and major drug-to-drug interaction. Continuing research is necessary to elucidate the pharmacological activities of herbal remedies now being used to treat diabetes mellitus.

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