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Diabetes mellitus and its treatment with some traditional herbs from the different districts of West Bengal: A Review

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Abstract: Diabetes is a group of metabolic diseases characterized by hyperglycemia that is due to the defects in insulin secretion, insulin action, or both. The chronic hyperglycemic effects of diabetes are associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetes mellitus may be observed with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop leading to stupor, coma and, in absence of effective treatment, death. In the present article 20 species of medicinal and aromatic plants have been identified with antidiabetic potential obtained from the state of West Bengal has been discussed.
Keywords: Diabetes mellitus, Medicinal and aromatic plants, insulin, decoctions

1. Introduction

Diabetes mellitus is a Chronic metabolic disorder that is characterised by a high concentration of blood glucose levels known as hyperglycaemia where the fasting plasma glucose is more than 7.0 mmol/l, or plasma glucose is more than 11.1 mmol/l 2 hours post meal. This is caused due to the deficiency of insulin secretion that may also include insulin resistance. This occurs when the hepatic glucose output is uncontrolled along with reduced uptake of glucose by the skeletal muscles coupled with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, then occurs a condition called glycosuria where glucose is spilled over into the urine, further there is osmotic diuresis known as polyuria that results in dehydration, increased desire of thirst, followed by increased drinking a symptom known as polydipsia. Deficiency of insulin results in wasting through increased breakdown and decreased synthesis of proteins. There may also occur diabetic ketoacidosis which is an emergency situation that develops in the absence of insulin whereby there is increased breakdown of fats into acetyl-CoA, which in the absence of aerobic carbohydrate metabolism, is converted to acetoacetate and β-hydroxybutyrate that causes acidosis and acetone. The role played by insulin in the pathogenesis of diabetes is worth mentioning. Insulin binds to a specific receptor on the surface of its target cells. The receptor itself is a large transmembrane glycoprotein complex belonging to the kinase-linked type 3 receptor superfamily and consists of two α and two β subunits. Occupied receptors get clustered, internalised in vesicles, causing down regulation. The signal transduction mechanism which brings about the biological effects of insulin are complex. The first step is receptor autophosphorylation that is a consequence of dimerisation allowing each receptors to phosphorylate the next. The insulin receptor substrate (IRS) proteins undergo rapid tyrosine phosphorylation in response to insulin and insulin like growth factors which are specific in nature, like IRS-1, that contains 22 tyrosine residues forming the potential phosphorylation sites. It further interacts with proteins containing the SH2 domain (a group of adapter proteins standing for Src homology after having been identified in the Src oncogene product), thus passing on the insulin signal. Further it has been shown that knockout mice lacking IRS-1 are hyporesponsive to insulin but as such do not become diabetic because of

robust B-cell compensation with high levels of insulin secretion whereas on the other hand mice lacking the IRS-2 develop diabetes overtly, thus making IRS-2 gene as a candidate for human type 2 diabetes[1].

1.1 Classification of Diabetes mellitus

Type 1 diabetes.

(β-cell destruction): In this type of diabetes mellitus there is absolute insulin deficiency also called as immune mediated diabetes. This form of diabetes, accounting for only 5–10% of the cases, previously known by the terms insulin dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. In this form of diabetes, the rate of destruction of β-cells varies, it is rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Ketoacidosis as the first manifestation of the disease occurs in some patients like children and adolescents others have modest fasting hyperglycemia switching over to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At the later stage of the disease insulin secretion is either very little or it ceases completely.Autoimmune destruction of β-cells is genetically related and is also associated with environmental factors that are still poorly defined. Some patients are rarely obese in this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia. The other form of diabetes in this category is idiopathic diabetes, which is strongly inherited, does not have immunological evidence for β-cell autoimmunity. Some of these patients have insulinopenia which is permanent and are prone to ketoacidosis, but have no evidence of autoimmunity.

Type 2 diabetes.

Either there is insulin resistance with relative insulin deficiency or predominantly an insulin secretory defect with insulin resistance. This form of diabetes, which accounts for almost 90–95% of those with diabetes also known as non–insulin dependent diabetes, type 2 diabetes, or adult-onset diabetes. In this category individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. The specific etiologies for this form of diabetes are not known, autoimmune destruction of β-cells does not occur. Most of the patients in type 2 diabetes are obese which to some extent causes insulin resistance. Ketoacidosis hardly occurs in this form of diabetes. This form of diabetes frequently goes undetected for many years because the hyperglycemia develops slowly and at earlier stages is not severe enough for the patient to notice any of the symptoms of diabetes. Patients develop microvascular and macrovascular complications as a result in this. Insulin resistance may improve with reduction in weight and/or pharmacological treatment of hyperglycemia but is hardly restored to normal levels. This form of diabetes develops with increasing age, obesity, and lack of physical activity.

Genetic defects of the β-cell.

Several types of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are often characterised by onset of hyperglycemia at an early age (generally before age 25years) and as such referred to as maturity onset diabetes of the young (MODY) and are characterized by impaired insulin secretion but insulin action may or may not be impaired. Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern in this form of diabetes. The resultant glucose intolerance is mild. Mutant insulin molecules are also produced with resultant impaired receptor binding abilities has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism[2].

Genetic defects in insulin action.

There are some unusual causes of diabetes resulting from genetically determined abnormalities of insulin action. The various metabolic abnormalities associated with mutations of the insulin receptor ranges from hyperinsulinaemia and modest hyperglycaemia to symptomatic diabetes [3][4]. Some individuals with these mutations are seen with acanthosis nigricans. Women develop virilization and have enlarged, cystic ovaries. In the past, this syndrome was termed Type A insulin resistance [3]. Leprechaunism and Rabson-Mendenhall syndrome are two paediatric syndromes that have mutations in the insulin receptor gene and as such alterations

in insulin receptor function and extreme insulin resistance are observed [4]. In the former case there are characteristic facial features while in the latter case there are abnormalities of teeth and nails and pineal gland hyperplasia.

Diseases of the exocrine pancreas.

Any process that causes injuries to the pancreas can cause diabetes. Acquired processes are pancreatitis, trauma, infection, pancreatic carcinoma, and pancreatectomy [5][6]. Damage to the pancreas must be extensive for diabetes to occur, with the only exception being cancer. However, adenocarcinomas which is involved only with a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in beta-cell mass [7]. If extensive enough, cystic fibrosis and haemochromatosis will also damage beta cells thereby impairing insulin secretion [8][9]. Fibrocalculous pancreatopathy may be accompanied by abdominal pain spreading to the back and pancreatic calcification on X-ray and ductal dilatation [10]. Pancreatic fibrosis and calcified stones in the exocrine ducts are found at autopsy.

Endocrinopathies.

Several hormones like growth hormone, cortisol, glucagon, epinephrine seem to antagonize insulin action. Diseases related with excess secretion of these hormones can cause diabetes for example Acromegaly, Cushing's syndrome, Glucagonoma and Phaeochromocytoma [11]. These types of hyperglycaemia typically resolve when the hormone which is in excess is removed. Somatostatinoma, and aldosteronoma-inducedhypokalaemia, can cause diabetes, probably by inhibiting insulin secretion [12][13]. Hyperglycaemia is resolved following successful removal of the tumour.

Drugs or chemical-induced diabetes.

Insulin secretion is also impaired by many drugs. These drugs may not, cause diabetes by themselves but they may aggrevate diabetes in persons with insulin resistance [14][15]. In such cases, the classification becomes unclear, as the significance of β-cell dysfunction or insulin resistance is unknown. Toxins like as Vacor (a rat poison) and pentamidine can permanently destroy pancreatic beta cells [16][17][18]. Fortunately, these drug reactions are rare. There are also many drugs and hormones which can impair insulin action. Examples include nicotinic acid and glucocorticoids [9][10]. These are given in table 1 below.

Table 1: Drugs and Chemicals inducing diabetes

1.	Nicotinic acids
2.	Glucocorticoids
3.	Thyroid hormones
4.	α- adrenergic agonists
5.	β- adrenergic agonists
6.	Thiazides
7.	Dilantin
8.	Pentamidines
9.	Vacor
10.	Interferon α- therapy

Infections.

There are certain viruses which are held responsible for β-cell destruction. Diabetes is seen in patients with congenital rubella, although most of these patients have HLA and immune markers hallmarks of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease [2].

Uncommon but specific forms of immune-mediated diabetes mellitus.

Diabetes is also associated with several immunological diseases with a pathogenesis or etiology different from that which leads to the Type 1 diabetes mellitus. Postprandial hyperglycaemia of a severity sufficient to fulfill the criteria for diabetes has been reported in some individuals who spontaneously develop insulin autoantibodies [19][20]. However, it is seen that in these individuals symptoms of hypoglycaemia occur

rather than hyperglycaemia. The "stiff man syndrome" is an autoimmune disorder of the central nervous system, characterized by stiffness of the axial muscles with painful spasms [21]. Affected people usually have high titres of the GAD autoantibodies and approximately one-half of the patients develop diabetes. Patients receiving interferon alpha have been reported to develop diabetes associated with islet cell autoantibodies and, in certain cases, severe insulin deficiency [22]. Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor thus reducing the binding of insulin to the target tissues [23]. Although, these antibodies can also act as an insulin agonist after binding to the receptor and thereby resulting hypoglycaemia [24]. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases [25].

Other genetic syndromes sometimes associated with diabetes.

Many genetic syndromes are followed by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of beta cells at autopsy [26]. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness. These and other similar disorders are listed in Table 2 below.

Table 2: Genetic syndromes associated with diabetes

1.	Down's syndrome
2.	Friedreich's ataxia
3.	Huntington's chorea
4.	Klinefelter's syndrome
5.	Lawrence-Moon-Biedel syndrome
6.	Myotonic dystrophy
7.	Porphyria
8.	Prader-Willi syndrome
9.	Turner's syndrome
10.	Wolfram's syndrome

Gestational diabetes mellitus

Since long, GDM has been defined as any degree of intolerance in the levels of glucose with onset or first recognition during pregnancy. In fact most cases resolve with delivery, the definition applied whether or not the condition persisted after pregnancy and includes the possibility that unrecognized glucose intolerance may have existed before or begun concomitantly with the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but its limitations were recognized for many years. As the current epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, the number of pregnant women with undetected type 2 diabetes has increased considerably [2].This category includes older women, those with previous history of glucose intolerance, women from certain high-risk ethnic groups, and any pregnant woman who has elevated fasting, or casual, blood glucose levels. It may be right to screen pregnant women belonging to high-risk populations during the first trimester of pregnancy so as to detect previously undetected diabetes mellitus. Formal systematic testing for gestational diabetes is usually done between 24 and 28 weeks of gestation [27].

This low-risk group comprises women who:

- are less than 25 years of age
- have a normal body weight
- have no family history (i.e., first-degree relative) of diabetes
- have no history of abnormal glucose metabolism
- have no history of poor obstetric outcome
- are not members of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic American, Native American, Asian American, African American, Pacific Islander)

1.2 Diagnosis of Diabetes mellitus.

When the diagnosis of diabetes is done, the clinician must be confident that the diagnosis is fully established because the consequences for the concerned individual are considerable and lifelong. Severe hyperglycaemia detected under conditions of acute infective, traumatic, circulatory or other stressful conditions may be transitory and should not in itself be regarded as a diagnosis for diabetes. The diagnosis of diabetes in an asymptomatic person should never be made on the basis of a single abnormal blood glucose value. For the asymptomatic person, a minimum of atleast one additional plasma/blood glucose test result with a value in the diabetic range is essential, either fasting, from a random sample, or from the oral glucose tolerance test (OGTT). If such samples fail to confirm the diagnosis of diabetes mellitus, it is generally advisable to maintain a record with periodic re-testing until the diagnosis becomes clear. In these cases, the clinician should take into consideration factors such as ethnicity, family history, age, adiposity, and concomitant disorders, before concluding on the diagnostic or therapeutic course of action. To make the diagnosis simpler an alternative to blood glucose estimation or the OGTT has long been sought. Glycated haemoglobin is an example, which reflects average glycaemia over a period of weeks, was thought to provide such a test. But in certain cases it gives equal or almost equal sensitivity and specificity to glucose measurement [28].

Criteria for the diagnosis of diabetes

1. A1C assay ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.

OR

2. FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

OR

3. 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).However it should be noted that in the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing [2].

1.3 Acute metabolic complications

Apart from hypoglycaemia diabetics are also susceptible to two major acute metabolic complications.

1.3.1. Diabetic ketoacidosis-

It occurs when insulin deficiency is coupled with a relative or absolute increase in glucagon concentration. It results from cessation of insulin intake and also from physical and emotional stress despite continued insulin therapy. In the former case the concentration of glucagon rises which is secondary to insulin withdrawal, but in stress it is epinephrine that is probably the operative stimulus. Apart from facilitating glucagon secretion it blocks the release of small amount of residual insulin found in some subjects with IDDM and inhibits insulin induced glucose transport in the peripheral tissues resulting in hormonal changes with multiple effects of which two are significant.

I) Maximal gluconeogenesis is induced thereby impairing the peripheral utilization of glucose resulting in severe hyperglycemia and
II) Activation of ketogenic process initiating development of metabolic ketoacidosis.

1.3.2. Hyperosmolar nonketotic coma-

It is basically a complication of non-insulin dependent diabetes, characterised by profound dehydration resulting from a sustained hyperglycemic diuresis under conditions in which the subject is unable to drink sufficient water to adjust the urinary fluid losses leading to infections, worsening hyperglycemia, preventing enough water intake and may be a stroke can also occur in this process.

1.4. Late complications of diabetes

A person suffering from diabetes is seen with a series of complications causing morbidity and premature mortality.

- Circulatory abnormalities
- Retinopathy
- Diabetic nephropathy
- Diabetic neuropathy
- Diabetic foot ulcers

Diabetes is also associated with cardiomyopathy wherein cardiac failure occurs, smoking is a major factor for both coronary and peripheral vascular disease and it should be avoided. Arteriosclerosis is also seen in diabetics which may be due to alterations in the ratio of high density to low density lipoproteins. Diabetic retinopathy is also observed in patients leading to blindness. Renal diseases is a very common complication and a leading cause of death in diabetes, here four types of lesions are described, glomerulosclerosis, arteriosclerosis of the efferent and afferent arterioles, arteriosclerosis of the renal artery and its intrarenal branches and peritubular deposits of glycogen, fats and mucopolysaccharides. Diabetic neuropathy on the other hand can injure every part of the nervous system possibly excepting brain, under such cases it may cause death, but it is a major cause of morbidity, most common is peripheral polyneuropathy symptoms include numbness, paresthesias, severe hyperesthesias followed by pain. Mononeuropathy seldom occurs characterised by sudden wrist drop, foot drop, including paralysis of the third, fourth and sixth cranial nerves. Further there is radiculopathy where pain occurs over the distribution of one or more spinal nerves usually in the chest wall or the abdomen. In autonomic neuropathy the gastrointestinal tract is the prime target the prime symptoms are difficulty in swallowing, diarrhea, delayed gastric emptying there can also be cardiorespiratory arrest leading to sudden death. A very significant problem arising out of diabetes is the development of ulcers of the feet and the lower extremities, these are due to abnormal pressure distribution secondary to diabetic neuropathy thus it becomes mandatory that all diabetics take proper foot care to prevent ulcers. The feet should therefore be checked daily for callus, infections, abrasions, any kind of blisters and if need arises patients are supposed to consult physicians without any loss of time [29]. Treatment of the disease is expensive when it is done with synthetic drugs but the economic burden on the subject may be reduced if plant based drugs are used.Many plants have been used in traditional systems of medicine for the oral treatment of diabetes like *Abelmoschus esculentus* [30][31], *Momordica charantia*, *Teucrium oliverianumi*, *Azadirachta indica*, *Galega officinalis*, *Globularia alypum*, *Punica granatum*. Antidiabetic activity has been found in the methanolic extracts of the rhizomes of *Acorus calamus*, it caused significant reduction in the fasting blood glucose levels in STZ induced diabetic rats at a dose of 200mg/kg of body weight [32], curcumin and turmeric have been shown to delay STZ induced diabetic cataract in rats [33], further leaf extracts of *Ficus glomerulata* was found to reduce the glucose levels in alloxan induced diabetes in rats [34]. Plants are well known in traditional herbal medicine for their antidiabetic activities, and available literature indicate that there are more than 800 plant species showing hypoglycemic activity [35]. Leaf extracts of *Ziziphus jujuba* also showed bloodsugar reducing activity [36]. There has been increase in the demand for the use of plant products with antidiabetic activity because of their low cost, easy availability and lesser side effects. Therefore, plant materials are continuously screened and explored for their effect as hypoglycemic agents.

Methodology

Extensive field work was done for the process of collection and identification in which different district of the state of West Bengal was visited for survey work which was based on the total area of all the blocks occurring under each district and the various plant specimens were thus collected and recorded. Tribal people along with local vaidyas, hakims, and shamans were consulted regarding the commonly used medicinal plants. To ascertain the use of these medicinal plants earlier published literatures of Bansal (2002), Suryanarayana *et al* (2005), Shirdel *et al* (2009), Sharma *et al* (2010), X Zhenzhong, and S. Hongjun (2010), Prisilla *et al* (2012) etc., were also followed. Spot identification was carried out for the species which were easily identifiable and growing in the area. The plant species which were not identified were collected and identified with herbarium from the Central national herbariums type section of BSI, WB. A documented herbarium of the species collected was prepared for further research work, these were then marked and deposited in West Bengal State Council of Science and Technology (WBSCST).

Results and Discussion

In the present study, 20 species of medicinal plants have been found to possess antidiabetic activities that are directly used by the local people. All the 20 species of the medicinal plants are presented below in Table – 3 along with the family they belong to, their local names, parts utilized, and uses. From the collected data, it is obvious that West Bengal has a very rich source of medicinal and aromatic plants of which many are used for treating diabetes mellitus. In most of cases, the local people seem to use leaves and bark of different species, roots, stems, and whole plant parts. Some are used if the form of decoctions, dusts of the plant parts and in other extractable forms. A lot of the vital informations about these medicinal and aromatic plants were also obtained from the local as well as tribal people including local baidyas, shamans, hakims etc.

Table 3

Slno.	Name	Family	Local name	Parts used
1.	*Abroma augusta* L.f.	Sterculiaceae	Ulatkambal	Leaves
2.	*Abelmoschus esculentus* L. Moench.	Malvaceae	Bhendi, Dharos	Fruits and seeds
3.	*Acacia farnesiana* Willd.	Fabaceae.	Guababla	Leaves and bark
4.	*Acacia nilotica* L. Del. Subsp. Indica (Benth) Brenan	Mimosaceae	Babla	Bark
5.	*Achyranthes aspera* L.	Amaranthaceae	Apang	Roots
6.	*Aconitum bisma* (Buch-Ham) Rapaics	Ranunculaceae	Bikhuma	Fresh and dry roots
7.	*Aconitum spicatum* (Bruhl.) Stapf	Ranunculaceae	Bikh	Roots
8.	*Acorus calamus* L.	Araceae	Boch	Rhizomes and roots
9.	*Aegle marmelos* L.	Rutaceae	Bel	Leaves
10.	*Aerva lanata* L. Juss. ex Schult	Amaranthaceae	Chaya	Whole plant
11.	*Alangium salvifolium* L.f. Wang.	Alangiaceae	Ankor	Leaves
12.	*Alpinia zerumbet* Pers. Burtt & Smith	Zingiberaceae	Elach	Fruit
13.	*Amaranthus spinosus* L.	Amaranthaceae	Kanta notey	Whole plant
14.	*Andrographis paniculata* (Burmf) wall. ex. Nees.	Acanthaceae	Kalmegh	Leaves
15.	*Argyreia nervosa* L.f	Convolvulaceae	Bidhora	Roots
16.	*Asparagus racemosus* Willd.	Asparagaceae	Satamuli	Vegetative roots
17.	*Azadirachta indica* A. Juss.	Meliaceae	Neem	Leaves
18.	*Biophytum sensitivum* L.	Oxalidaceae	Jhalai, Bon narenga	Whole plant and seed
19.	*Bixa orellana* L.	Bixaceae	Lotkon	Roots
20.	*Bombax ceiba* L.	Bombacaceae	Simul	Roots

Conclusion

With the increase in number of diabetic patients scientists are trying to find out new methods to treat diabetes. Inspite of the presence of known anti diabetic agents in the pharmaceutical market remedies obtained from the medicinal plants are used with success to treat this dangerous disease. Since many herbs and plants have been described as possessing hypoglycemic activity the efficacy of herbal drugs in the treatment of diabetes is significant and they have fewer side effects than the synthetic allopathic medicines. Further, phytochemical characterisation of medicinal plants are required to identify the specific compound(s) involved in the observed hypoglycemic effect so that they can be utilised for the benefit of mankind.

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