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A Brief Review of Indigenous Medicinal Plants and Their Role in the Management of Diabetes Mellitus

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ABSTRACT

Diabetes Mellitus is a group of metabolic diseases in which there are high blood sugar levels over a continuous period. Diabetes mellitus is widely recognized as one of the leading causes of death and disability. Insulin insensitivity, pancreatic β cell function declines, and obesity is the phenomenon of clinical hyperglycemia. Several mechanisms have been proposed to be responsible for insulin resistance, including increased non-esterified fatty acids, inflammatory cytokines, adipokines, and mitochondrial dysfunction, as well as glucotoxicity, lipotoxicity, and amyloid formation for β-cell dysfunction. Moreover, the disease has a strong genetic component, although only a handful of genes have been identified so far. Diabetic management includes diet, exercise, and combinations of antihyperglycemic drug treatment with lipid-lowering, antihypertensive, and antiplatelet therapy. Traditionally, there are some medicinal plants believed to treat diabetes, as they have been proven in research studies to possess anti-diabetic properties, such as improved insulin sensitivity and hypoglycemic activities, due to their high level of phenolic compounds, flavonoids, terpenoids, alkaloids, and glycosides. A review has been conducted to identify potential medicinal plants used in India for type2 diabetic individuals and to potentially identify any bioactive compounds involved in electively treating symptoms of diabetes. This review focuses on diabetic Mellitus and the indigenous plant and their components used in the treatment of diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder, resulting from insulin deficiency, characterized by an abnormal increase in the blood sugar level, altered metabolism of carbohydrates, protein, and lipids, and an increased risk of vascular complications[1]. As per World Health Organization, DM is characterized by common features of chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism[2]. There are numerous pathogenic processes involved in the development of diabetes. This includes autoimmune destruction of the β-cells of the pancreas which leads to consequent insulin deficiency and abnormalities that result in resistance to insulin action. The deficiency of insulin on target tissues causes abnormalities in carbohydrates, fat, and protein. The causes were not well understood until the 19th century when Paul Langerhans, a German medical student discovered what has become known as the islets of Langerhans which produce insulin. Insulin is a protein hormone that promotes the uptake of glucose by the body's cells. Treating diabetes has always been difficult and prior to the 1920s, the primary treatment plan was controlling diet. In 1921, Dr. Frederick Banting discovered how to extract insulin from cattle that could be used as an injectable form for human diabetics which revolutionized the treatment of the disease and made it more manageable. Untreated, diabetes can cause a number of health problems including, blindness, loss of circulation resulting in limb amputation, high blood pressure, heart disease, and kidney failure.

It has been observed that 2.8% of the world's population suffers from this disease and it is expected to increase to more than 5.4% by 2025 [3]. Diabetes requires early diagnosis, treatment, and lifestyle changes. Diabetes is a disease that affects many people in the 21st century and is known as the fifth leading cause of death [4]. High prevalence, variable pathogenesis, progressive process, and complications of diabetes all highlight the urgent need for effective treatments. Nowadays, different treatments, such as insulin therapy, pharmacotherapy, and diet therapy, are available to control diabetes. There are several types of glucose-lowering drugs that exert anti-diabetic effects through different mechanisms. These mechanisms include stimulation of insulin secretion by sulfonylurea and meglitinides drugs, increasing of peripheral absorption of glucose by biguanides and thiazolidinediones [5], delay in the absorption of carbohydrates from the intestine by alpha-glucosidase, and reduction of hepatic gluconeogenesis by biguanides [6]. In the past three decades, despite the significant progress made in the treatment of diabetes, the results of treatment in patients are still far from perfect. These treatments have some disadvantages, including drug resistance

(reduction of efficiency), side effects, and even toxicity. Sulfonylureas which is used as an antidiabetic drug lose their effectiveness after 6 years of treatment in 44% of patients. It is also said that the glucose-lowering drugs are not able to control hyperlipidemia [7] In addition, the side effects of medicines and their interactions with each other *in vitro*must be considered by medical staff. Today, many treatments that involve the use of medicinal plants are recommended [8]. Most plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and can often have anti-diabetic effects [9]. The anti-hyperglycemic effects that result from treatment with plants are often due to their ability to improve the performance of pancreatic tissue, which is done by increasing insulin secretions or reducing the intestinal absorption of glucose. The main purpose of this article is to introduce a number of effective medicinal plants used for treating diabetes and other mechanisms of plant compounds used to reduce glucose levels and increase insulin secretion.

Prevalence

The number of people with diabetes is increasing due to population growth, aging, urbanization, and the increasing prevalence of obesity and physical inactivity. [10]The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people 65 years of age[11].

Types of Diabetes [12]

1) Type 1 diabetes (insulin-dependent diabetes, juvenile diabetes, early-onset diabetes): The body does not produce insulin. People usually develop type 1 diabetes before their 40thyear, often in early adulthood or teenage years.

2) Type 2 diabetes: The body does not produce enough insulin for proper function, or the cells in the body do not react to insulin (insulin resistance). Approximately 90% of all cases of diabetes worldwide are type 2.

3) Gestational diabetes: This type affects females during pregnancy. Some women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to

transport all of the glucose into their cells, resulting in progressively rising levels of glucose. The majority of gestational diabetes patients can control their diabetes with exercise and diet.

4) Other specific types of diabetes mellitus: [13]

• genetic defects of ß-cell function

• genetic defects in insulin action

• diseases of the exocrine pancreas

• other endocrinopathies

• drug- or chemical induced diabetes mellitus

• infection-induced diabetes mellitus

• rare forms of immune-mediated diabetes

• other genetic syndromes sometimes associated with diabetes

Diagnosis of Diabetes Mellitus

Two replicate fasting glucose levels that exceed 126 mg/dl (>7 mmol /L) are consistent with diabetes even in the absence of symptoms. Normal fasting blood glucose levels of 100 mg/dl or above are considered impaired fasting glucose (IFG). Persons with IFG levels (FPG= 100-125 mg/dl (5.66.9 mmol/l) and/or with impaired glucose tolerance test (IGT) (2 hours post-load glucose 140-199 mg/dl (78.8 mmol /L-11.1 mmol/L) are at risk of diabetes and should be observed periodically to detect hyperglycemic progression. Replicate, two-hour glycemic responses >200 mg/dl (>11.1 mmol/L) after a standard oral glucose tolerance test also indicate diabetes. This stage is often reached before the fasting glucose levels rise in T2DM and post-prandial hyperglycemia may precede fasting hyperglycemia by months to years. The reliance on only fasting glucose levels is generally more useful for the identification of impending T1D but not for T2D.

Complications

The possible complications that can be caused by badly controlled diabetes are 1) Eye complications - glaucoma, cataracts, diabetic retinopathy, and some others. 2) Foot complications - neuropathy, ulcers, and sometimes gangrene which may require that the foot

be amputated 3) Skin complications - people with diabetes are more susceptible to skin infections and skin disorders 4) Heart problems - such as ischemic heart disease, when the blood supply to the heart muscle is diminished 5) Mental health - uncontrolled diabetes raises the risk of suffering from depression, anxiety and some other mental disorders 6) Hearing loss - diabetes patients have a higher risk of developing hearing problems 7) Gum disease - there is a much higher prevalence of gum disease among diabetes patients 8) Erectile dysfunction - male impotence. 9) Infections - people with badly controlled diabetes are much more susceptible to infections 10) Healing of wounds - cuts and lesions take much longer to heal.

Pathophysiology

An increase in blood glucose concentration conducts to the loss of water in cells, along with osmosis, to blood. Whenever the blood glucose level increases the pancreas responds by secreting insulin. [14]. Prospective studies suggest that the main pathophysiological defects leading to type 2 diabetes are insulin resistance and a relative insulin secretory defect. The main aetiological risk factors are age, obesity, family history, and physical inactivity. Dietary risk factors have recently emerged: risk is increased by high consumption of red and processed meat and sugar-sweetened beverages, and reduced by intake of fruit and vegetables, some types of dairy products, and some overall dietary patterns. Type 1 Diabetes Mellitus- Type 1 diabetes mellitus (T1DM) comprises several diseases of the pancreatic ß cells which lead to an absolute insulin deficiency. This is usually considered to be the result of autoimmune destruction of the pancreatic ß cells (type 1A). Some patients with T1DM with no evidence of ß cell autoimmunity have underlying defects in insulin secretion often from inherited defects in pancreatic ß cell glucose sensing and from other genetic or acquired diseases. Type 2 Diabetes Mellitus- Type 2 diabetes mellitus (T2DM) is by far the more common type of diabetes and is characterized by insulin resistance resulting from defects in the action of insulin on its target tissues (muscle, liver, and fat), but complicated by varying and usually progressive failure of beta cells' insulin secretory capacity. Most patients with T2DM in the US and Europe are overweight or obese, however, in India and China, most T2DM patients have a lean body mass index (BMI), albeit with increased visceral and hepatic fat.

Current treatments for diabetic Mellitus and their side effects

Commonly used pharmacological agents for the treatment of T2D include drugs from different classes such as biguanides (ex. metformin), sulfonylureas (ex. glyburide and glipizide), meglitinides (ex. repaglinide and nateglinide), and thiazolidinediones (ex. pioglitazone). The drugs belonging to these classes are administered as the first line of defense to prevent deterioration of the diabetic state.

Insulin is a hormone, produced by the pancreatic β cells in the body and regulates the body's sugar level in the bloodstream as well as allowing excess glucose to be stored in the liver. Although T2D patients produce their own insulin as the disease progresses, either the amount of produced insulin is not enough or there is a further low response towards insulin in target cells of these patients. Hence, in most cases, insulin therapy is chosen as the final step for glucose-lowering therapies [15]. The major disadvantages associated with long-term use of insulin therapy are hypoglycemia and weight gain. These symptoms are very well justified because there is a decrease in glycosuria and less energy consumption in these patients as the glycemic level is improved by this therapy. Apart from insulin the other commonly used pharmacological agents for the treatment of T2D include drugs from different classes such as biguanides (ex. metformin), sulfonylureas (ex. glyburide and glipizide), meglitinides (ex. repaglinide and nateglinide), and thiazolidinediones (ex. pioglitazone). The drugs belonging to these classes are administered as the first line of defense to prevent deterioration of the diabetic state[16]. One of the main side effects of activation of the PPAR γ receptors (Thiazolidinediones) is the enhanced proliferation of peripheral adipocytes to increase uptake of free fatty acids. This effect may adversely lead to weight gain and increased peripheral fat mass [17]. Several recent studies and analyses have revealed the potential impact of TZD on cardiovascular events in patients with type 2 diabetes. Metformin is known to decrease pyruvate dehydrogenase activity and hence leads to lactic acidosis, which is a rare but potentially fatal complication associated with the use of metformin. The increased risk of metformin-induced lactic acidosis generally arises in patients with renal, pulmonary or cardiac insufficiency or with a history of liver disease. Sulfonylureas and its derivatives which are used for the treatment of diabetics are associated with an increased cardiovascular risk[18].

Complementary treatments for the management of diabetics

The risks associated with the use of conventional anti-diabetic agents are high. Based on literature it has been proved that in some cases synthetic drugs may produce toxic and may adversely affect the health of the patient. Hence some complementary treatments are adopted these are-

Exercise- It is a well-known fact that frequent and regular exercise boosts the overall quality of life and is likely to prevent various lifestyle-associated diseases like cardiovascular disease, obesity, and T2D [19].

Yoga – It is a physical and spiritual exercise regimen that holds immense potential as a co-intervention in the improvement in the quality of life for diabetic patients. It involves various body postures and movements (known as asanas), breathing techniques, and meditation, which are all designed to promote physical comfort and mental composure. [20].

Diet- It is considered the most vital factor governing the health of an individual. There are ample studies suggesting the significance of diet for a healthy life. Studies have shown that low-fat vegetarian diets consisting of fruits, vegetables; grains, etc. are associated with increased insulin sensitivity, glycemic control, weight loss, etc., and thus help to control diabetics[21].

Vitamins- It has been suggested that vitamins have a strong potential to cure diseases like T2D when given as a supplement. It has been hypothesized that diabetes is a disease marked by oxidative damage [22]. So there is a significant association between antioxidants and oxidative stress. On the other hand, many of the vitamins such as vitamins D, C, and E are known potential antioxidants, hence could be used to cure diabetes by lowering oxidative stress [23].

Medicinal plants used for the treatments for the management of diabetics- [24]

1. Giloy- The leaves of the plant play a major role in stabilizing blood sugar levels and controlling diabetes. It helps to boost immunity.

2. Vijaysar-It is the anti-hyperlipidemic properties of this herb that help reduce total cholesterol, low-density lipoprotein, and serum triglyceride levels in the body. Moreover, it helps reduce the symptoms associated with diabetes that include frequent urination, overeating, and burning sensation in the limbs.

3. Fenugreek seeds: (*Trigonellafoneum-graecum*) - Fenugreek seeds are high in soluble fiber, which helps lower blood sugar by slowing down digestion and absorption of carbohydrates. This suggests they may be effective in treating people with diabetes.

4. *Gymnema sylvestre*(Gurmar) - It is one of the most powerful herbs, it blocks the absorption of glucose in the small intestine. Gymnemic acid boosts the production of insulin in the pancreas, which helps the body naturally support blood sugar, reduce sugar cravings and manage weight.

5. *Curcuma longa*(Turmeric) - It helps as adjuvant therapy for the prevention and treatment of diabetic encephalopathy. Its active ingredient is curcumin.

6. Cassia Fistula (Green tea) - It exhibits hypoglycemic, glucose oxidizing, and insulin-mimetic activities. Its active ingredient is Catechin.

7. *Ocimum sanctum*: (holy basil) - It is commonly known as Tulsi. It showed a significant reduction in blood sugar levels 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 indicated the hypoglycemic and hypolipidemic effects of tulsi in diabetic rats.

8. *Momordica charantia*: (bitter gourd)

Momordica charantia is commonly used as an antidiabetic and antihyperglycemic agent. Extracts of fruit pulp, seed, leaves, and the whole plant were shown to have hypoglycemic effects in various animal models.

9. *Aegle marmelos*: It is commonly known as Bael or Sirphal, is a medium-sized tree found wild, especially in dry forests, and is also cultivated throughout India. The leaves produced significantly controlled blood glucose, urea, body weight, liver glycogen, and serum cholesterol.

10. *Murraya koeingii*: It is commonly known as Kurrypatta, it showed hypoglycemic effects associated with increased hepatic glycogen content due to increased glycogenesis and decreased glycogenolysis and gluconeogenesis.

11. *Ficus bengalenesis*: It is commonly known as the Indian Banyan tree or Bur, which is a Very large tree distributed throughout India from sea level to 1.200 m. It yields latex-

containing Caoytchoue (2.4%), Resin, Albumin, Cerin, Sugar, and Malic acid. It is having potent hypoglycaemic action.

12. *Panax ginseng*: These are slow-growing perennial plants with fleshy roots. The root of ginseng has been used for over 2,000 years in the Far East for its health-promoting properties. It is found to contain triterpene glycosides, or saponins commonly referred to as ginsenosides, polysaccharides, peptides, polyacetylene alcohol, and fatty acids. It showed a decrease in the level of blood sugar and liver glycogen when injected intravenously into rats.

13. *Eugenia jambolana*– It is commonly known as Jamun or black plum, is being widely used to treat diabetes by traditional practitioners over many centuries.

14. *Picrorrhiza kurroa*– It is commonly known as Kutki in India, is a small herb found in the Himalayan region from Kashmir to Sikkim. Dried rhizomes of the plant are being used for medical treatment. Recently, it has been known that alloxan induces its diabetogenic activity mainly by inducing oxygen free radicals and thereby damaging the International Bulletin of Drug Research.

15. *Psidium guajava*- It is commonly known as Guava or Amrood, is a semi-deciduous tropical tree in north India and is widely grown throughout India for its fruits. It is found to contain a high percentage of vitamin C, carotene, Vit B1, B2, B6, and free sugars (glucose, fructose, and sucrose).

16. *Lawsonia inermis*– It is commonly known as Henna or Mehendi, is a much-branched glabrous shrub or small tree, cultivated for its leaves is found to constitute carbohydrates, proteins, flavonoids, tannins, phenolic compounds, alkaloids, terpenoids, quinones, coumarins, xanthones, and fatty acids. Ethanol (70 %) extract of *L. inermis* showed significant hypoglycaemic and hypolipidaemic activities in alloxan-induced diabetic mice after oral administration.

17. *Cinnamomum zeylanicum*- It is commonly known as Cinnamon, is harvested by growing the tree for two years then coppicing it. They mainly constitute volatile oils, containing cinnamaldehyde. Cinnamon ingestion reduced total plasma glucose responses International Bulletin of Drug Research. Cinnamon supplementation may thus be important *in vivo* glycaemic control and insulin sensitivity in humans and they also appear to be sustained for 12 hours.

Susceptibility Genes responsible for diabetic Mellitus

A large number of susceptibility genes in varying combinations conspire with environmental factors to give rise to the final pathophysiological pathways of insulin resistance and secretion defects. Even though several hundred susceptibility loci for T2D have been identified using genome-wide association studies (GWAS), they account for only about 20%–30% of the heritability of T2D, with the remaining "missing heritability" being attributed to rare or small-effect variants, epistasis, gene-environment interaction epigenetic changes, etc. [25] It has been observed that activation of oxidative stress pathways plays a key role in the development of not only the late complications (such as cardiovascular disease, nephropathy, retinopathy, and amputations) in DM1 and DM2 but also in the early stage such as insulin resistance. There are many sources of reactive oxygen species (ROS) production in diabetes including mitochondrial and nonmitochondrial origins: NADPH oxidase, xanthine oxidase, uncoupled eNOS, lipoxygenase, cyclooxygenase, cytochrome P450 enzymes, and other hemoproteins, and mitochondrion is thought to be the main source of ROS generation site in DM. [26]A few studies claimed that the susceptibility genes are HLA, PTPN22, IL2Ra, CD8, CD4, and CTLA-4. PTPN22 encodes a member of the non-receptor class 4 subfamily of the protein-tyrosine phosphatase family. The encoded protein is a lymphoid-specific intracellular phosphatase that associates with the molecular adapter protein CBL and may be involved in regulating CBL function in the T-cell receptor signaling pathway. Mutations in this gene may be associated with a range of autoimmune disorders including Type 1 Diabetes. The interleukin 2 (IL2) receptor alpha (IL2RA) and beta (IL2RB) chains, together with the common gamma chain (IL2RG), constitute the high-affinity IL2 receptor. Homodimeric alpha chains (IL2RA) result in the low-affinity receptor, while homodimeric beta (IL2RB) chains produce a medium-affinity receptor. The alpha chain of the IL-2 receptor complex is an essential molecule indicated on T cells upon the operation and on natural Tregs at baseline. CTLA-4 is a member of the immunoglobulin superfamily and encodes a protein that transmits an inhibitory signal to T cells. The protein contains a V domain, a transmembrane domain, and a cytoplasmic tail. Alternate transcriptional splice variants, encoding different isoforms, have been characterized. The membrane-bound isoform functions as a homodimer interconnected by a disulfide bond, while the soluble isoform functions as a monomer. Mutations in this gene have been associated with insulin-dependent diabetes mellitus. The CD8 antigen is a cell surface glycoprotein found on most cytotoxic T lymphocytes that mediate efficient cell-cell interactions within the immune system. The CD8

antigen acts as a coreceptor with the T-cell receptor on the T lymphocyte to recognize antigens displayed by an antigen-presenting cell in the context of class I MHC molecules. The coreceptor functions as either a homodimer composed of two alpha chains or as a heterodimer composed of one alpha and one beta chain. Both alpha and beta chains share significant homology to immunoglobulin variable light chains. This gene encodes the CD8 alpha chain. Multiple transcript variants encoding different isoforms have been found for this gene.[27]The major protein isoforms of this gene differ by the presence or absence of a transmembrane domain and thus differ in being a membrane-anchored or secreted protein. Glutamate decarboxylase catalyzes the production of GABA. It was identified as a major antigen in insulin-dependent diabetes. It is also responsible for catalyzing the production of gamma-aminobutyric acid from L- glutamic acid. Gamma-aminobutyric acid is synthesized by two isoforms of pyridoxal 5'phosphate-dependent enzyme glutamic acid decarboxylase. It was also identified as an autoantibody and autoreactive T cell target in insulin-dependent diabetes. The main ones are islet cell autoantibodies, insulin autoantibodies, autoantibodies targeting the 65-kDa isoform of glutamic acid decarboxylase, autoantibodies targeting the phosphatase-related IA-2 molecule, and zinc transporter autoantibodies.[28]

CONCLUSION

Diabetes mellitus is a complicated health condition with multiple causes and many treatment options. Various myths may influence diabetics' health-seeking behavior, and they may use traditional medicines, which include normal foods and herbs, for primary health care. Plants are natural antioxidants and effective herbal medicines, in part due to their anti-diabetic compounds, such as flavonoids, tannins, phenolic, and alkaloids that improve the performance of pancreatic tissues by increasing the insulin secretion or decreasing the intestinal absorption of glucose. More research is required in order to isolate the active components of plants as a whole or parts of the plant and molecular interactions of their compounds for analysis of their curative properties.

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