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A review on diabetes mellitus and diabetic neuropathy: A plant based approach

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Abstract
Diabetes mellitus is one of the most non communicable disease globally. Scientific reports reveal that diabetes can't be cured completely. Allopathic medicine haven't showed ay significant effect for the complete cure of the disease.Hence focus has been turned towards traditional system of medicine. The present review gives detailed information about diabetes mellitus and its associated complication diabetic neuropathy and various medicinal plants used in the treatment of disease

Keywords: Diabetes mellitus, hyperglycaemia, polyol pathway, neuropathy, medicinal plants

1. Introduction
Diabetes mellitus [1] is a heterogenous metabolic disorder characterized by common feature of hyperglycaemia with disturbance of carbohydrate metabolism, fat and protein metabolism, It is the sixth leading cause of disease related death in the world. Diabetes mellitus can produce macrovascular complications like diabetic neuropathy, nephropathy, retinopathy etc. Diabetic neuropathy is the complication of diabetes affecting nervous system; which affect the circulation of blood in the legs, contributing to the risk of diabetes related foot problem. Allopathic medicines are not effective in treating the disease leading to various adverse effects. Herbal medicines are currently in demand and their necessity is increasing eventually. Leguminose, Lilliaceae, Cucurbitaceae, Asteraceae, Rosaceae, Euphorbiaceae, Polygallaceae etc. are the plant families confirmed to show hypoglycemic activity. Many clinical studies have conformed the therapeutic importance of medicinal plants in the treatment of diabetic mellitus.
The effect of medicinal plants may delay the diabetic complications and rectify the metabolic abnormalities. They showed hypoglycemic activity with more efficacy [2].
Type 1 diabetes mellitus (T1DM) is one of the most common endocrine and metabolic conditions in childhood. Factors have long been implicated in the pathogenesis of T1DM both as initiator and potentiators of pancreatic β-cells destruction.Type 2 Diabetes mellitus (T2DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia, which results from resistance to insulin actions on peripheral tissues as well as inadequate secretion of insulin and an impaired suppression of glucagon secretion in response to ingested glucose. [3] Diffuse neuropathy [6] is a kind of nerve problem that affects many part of the body. Peripheral neuropathy affects feet and hand. Autonomic neuropathy affects the internal organs. Autonomic neuropathy can affect many of body processes and systems, everything from sexual response in both women and men, digestive problems that cause weight loss, regulation of body temperature [7] and sweat. Proximal type causes pain usually on one side in the thighs, hips or buttocks. It can also leads to weakness in the leg

Pathophysiology
Insulin is the principle hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver and gluconeogenesis the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. Insulin is released into the blood by beta-cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating.

Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage.Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin. If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic defects, such as acidosis. When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss.

Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia) [8]

Polyol pathway [9] is responsible for producing lesions in the aorta, lens of the eye, kidney and peripheral nerves. These tissues have an enzyme, aldose reductase that reacts with glucose to form sorbitol and fructose in the cells of hyperglycemic patient

Glucose+ NADH+H^+	aldose reductase	sorbitol+ NAD^+
Sorbitol+ NAD	sorbitol dehydrogenase	fructose+ NADH+H^+

Intracellular accumulation of sorbitol and fructose so produced results in the entry of water inside the cell and consequent cellular swelling and cell damage. Also intracellular accumulation of sorbitol causes intracellular deficiency of myo-inositol which promotes injury to Schwann cells and retinal pericytes. This polyol results in disturbed processing of normal intermediate metabolites leading to complications of diabetes

Various Plants for the Treatment

Artemesia Pallens [10] is commonly called as davana belonging to Compositae family.

Methanolic extract of aerial parts are responsible for anti - diabetic activity. They inhibit glucose absorption and increase peripheral glucose utilization. Davanone, divan ether, divan furan and linalool are the major constituent. Aegele Marmelos commonly called holy fruit tree belonging to Rutaceae family. Aegelin, ɑ and β-sitosterol marmalosin, marmesin are the constituents responsible for anti-diabetic activity. It increases utilization of glucose either by direct glucose stimulation or by acting like insulin like glucose for uptake. Allium Sativa is commonly called as garlic, belongs to family Alliaceae. Anti-hyperglycemic activity was observed in ethyl acetate, ethanol and petroleum ether extract of alloxan induced rabbits. Allium, epigenin, allicin-s-allyl cysteine sulfoxide is responsible for hypoglycemic activity. It has been found that ethyl acetate extract is most potent and active principle producing maximum hypoglycemic activity due to increased insulin. Occimum Santum is commonly called thulsi belonging to Labiatae family. Leaf powder extract was glucose lowering activity. In streptozotocin induced diabetic animals the effect of the extract on three enzymes of carbohydrate metabolism namely glucokinase, hexokinase and phospofructokinase has been revealed. Eugenol, carvacol, linalool, caryophylline, β-sitosterol present in occimum santum has potent hypoglycemic effect in normal and diabetic rats. Administration of leaf extracts leads to decrease in plasma glucose level by 24.6%. Gymnema Sylvestre commonly known as madhunashini belonging to family Asclipidaceae. Its leaves has been widely used in ayurvedic traditional medicine and is bitter, acrid, thermogenic, anti-inflammatory, anodyne, anticancer properties. Gymnemic acid is the chief constituent responsible for anti-diabetic effect. Gymnemic acid [11] has the ability to delay the glucose absorption in the blood. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. That molecule fills the receptor locations on the taste buds thereby preventing its activation by sugar molecules present in the food. Similarly Gymnemic acid molecules fill the receptor location in the absorptive external layer of the intestine thereby prevents the absorption of sugar molecule by the intestine which results in decreased blood sugar. When Gymnema leaf extract is administered in a diabetic patient there is a stimulation of the pancreas by virtue of which there is an increase in insulin release. I t is believed that by inhibiting sweet taste sensation people taking this will limit their intake of sweet foods and this activity is partially responsible for its hypoglycemic effect. Possible mechanism by which they exert hypoglycemic effects; increases insulin secretion, promotes regeneration of islet of cells, increases the utilization of glucose; it is shown to increase the enzyme responsible for utilization of glucose, by insulin dependent pathway and increase in Phosphorylate activity, decrease in gluconeogenic Enzymes and sorbitol dehydrogenase causes the inhibition of glucose absorption from intestine. Momordica Charantia [12-14] commonly called as bitter guard belonging to family Cucurbitaceae. It is a popular herbal resource to treat diabetes. Charantin (mixture of sterol glycosides), vicine (pyrimidine nucleotide) and p-insulin (polypeptide) are reported as active ingredients. It is most studied with regard to antidiabetic effect and all part of plant show hypoglycemic activity in normal animals. A polyhedral preparation containing Momordica charantia show a significant reduction in blood glucose, glycosylated haemoglobin and an increase in plasma insulin and total haemoglobin in animals. Ethanolic extract of Momordica charantia achieved nearly euglycemic state within 2 weeks of treatment. The pulp juice and saponin free methanolic extract of juice from fruit exerted significant hypoglycemic effect in fasting and post prandial states of normal and non-insulin dependent diabetes mellitus (NIDDM) rats. Momordica charantia has been shown to enhance the number of β-cells. Another study shows that momordica charantia can act like insulin or promote insulin release. Other studies shows that hypoglycemic effect is due to an extra pancreatic effect which includes GLUT4 transporter proteins in muscle, increased glucose utilization in the liver and muscle, inhibition of glucose 1, 6-bisphosphatase and glucose-6-phosphatase in liver and stimulation of red cell,

hepatic glucose-6-phosphate dehydrogenase activity which contributes to hypoglycemic activity of Momordica charantia by inhibiting the glucose transport at the brush border of small intestine. Depressed carbohydrate enzyme activity in liver of diabetic mice was restored with momordica charantia treatment (hexokinase, glucokinase, and phosphofructokinase. Administration of Momordica charantia would lead to the secretion of insulin from endocrine pancreatic β- cells.

Momordica charantia significantly increased the number of β-cells compared to untreated diabetic rats. Momordica charantia juices may have a role in the renewal of β-cells in treated diabetic rat; alternatively the juice may permit the recovery of partially destroyed β-cells. Momordica charantia and its extracts may possess cell like proliferation and growth like properties similar to that of insulin. In treated diabetic rat, chrantia increases the myelinated fiber area and myelin area. Administration of momordica charantia not only reduced blood glucose level but also corrected the structural abnormalities of peripheral nerves. Momordica charantia also has potent aldose reductase inhibitory activity in diabetic rats leading to slight increase in the myelinated fiber area. Coptis Chinensis Franch [15] dried rhizome of Coptis chinensis Franch belonging to the family Ranunculaceae is traditionally used in the Chinese medicine for the treatment of diabetes and inflammatory diseases. The alkaloid obtained from these plants has neuroprotective, neurogenerative, anti-diabetic, anti-oxidative and anti-inflammatory effects. The alkaloids present are berberine, palmatine, hydrastine and copistine. The study shows a significant reduction in cell viability, increased apoptotic rate, declined mitochondrial membrane potential and increased ROS (reactive oxygen species) production. Due to this neuroprotective properties, Coptis chinensis Franch might be a potential therapeutic agent for the prevention or amelioration of diseases like diabetic neuropathy and neurodegenerative disorders like Alzheimer's and Parkinson's disease. Calotropis Procera [16] is one of the ancient traditional shrubs which have been used for the treatment of diabetes, pain and inflammation. The root extract of Calotropis procera is used for the treatment of diabetic neuropathy. The negative control rats developing diabetes and diabetic neuropathy after 6 weeks of streptozotocin administration were distinguished by significant hyperalgesia and tactile allodynia with enhanced HbA1c% level compared to normoglycemic rats. Momordica Cymbalaria: [17] ethno botanical information reports around 800 plants that may possess anti-diabetic activity when assessed using presently available techniques. Momordica cymbalaria Fenzl belongs to the family Cucurbitaceae; is a species found in Karnataka and Andhra Pradesh. Its tuber is traditionally used as abortifacient and also for the treatment of diabetes mellitus, its fruit powder and extract were reported to have anti-diabetic activity in experimental type-1 diabetes mellitus. The anti-diabetic activity of saponins of Momordica cymbalaria is possibly due to reversal of the atrophy of the pancreatic islets of β-cells resulting in increased insulin secretion and hepatic glycogen levels which may attenuate hyperinsulinemia. The α-adrenergic blocking effect may also contribute to their insulin secretion and sensitizing effects. Steroidal saponin of Momordica cymbalaria revealed significant preventive or curative effects on diabetic neuropathy due to improvement in myelination and restoration of neuronal integrity, thereby delaying the progression of neuropathy. The neuronal anti - oxidant activity may facilitate the neuroprotective effect. Diosmin [18] is a type of plant chemical found mainly in citrus plant. Diosmin is a flavone, a member of the flavonoid family. Treatment with diosmin at doses of 50 and 100mg/kg significantly restored the reduced body weight, elevated blood sugar and lipid proliferation. Further dose dependent improvement was observed in thermal hyperalgesia, cold allodynia and walking function in diabetic rats administered with diosmin. Elevated levels of malondialdehyde and nitric oxide and decreased glutathione levels and superoxide dismutase activity in diabetic rats were restored significantly after 4 weeks of diosmin treatment. Increased level of malondialdehyde and nitric oxide causes oxidative stress, thereby decreasing their level leads to protective effect. Diosmin has shown beneficial effect in preventing the progression of early diabetic neuropathy in diabetic rats. Ginger [19] Diabetes mellitus results in neuronal damage caused by increased intracellular glucose leading to oxidative stress. Recent evidence revealed the potential of ginger for reducing diabetic induced oxidative stress markers. The studies revealed a protective role of ginger mediated by modulating the astroglial response to the injury, reducing Ach expression (acetylcholine) and improving neurogenesis. The results represent a new insight to the beneficial effects of ginger on structural alterations of diabetes brain and suggest that ginger might be a potential therapeutic source for the treatment of diabetic induced damage in the brain. Evening Primrose Oil And Alpha-Lipoic Acid; [20-22] treatment with α-lipoic acid or evening prim rose oil, individually fails to prevent diabetes induced changes in enteric nerves. Since synergy between these treatments has been reported, the aim was to investigate the effectiveness of combined LA/EPO (lipoic acid/evening prim rose oil) treatment. Nerves supplying the ileum containing vasoactive intestinal peptide [VIP], calcitonin gene related peptide [CGRP] and nor adrenaline [NA] were examined biochemically. Diabetes caused a significant increase in VIP containing cell bodies, decrease in noradrenaline content and loss of CGRP immunoreactivity LA/EPO treatment totally prevented diabetes induced changes in VIP and CGRP and partially reversed these changes. In contrast treatment had no effect on diabetes induced changes in NA containing nerves because these nerves are resistant to treatment. Therefore LA/EPO is only effective at treating diabetes induced changes in some enteric nerves when demonstrated in combination. Impaired nerve perfusion is an important factor in the development of diabetic peripheral neuropathy. Reduced nerve oxygen tension has been demonstrated and also decreased sural nerve blood flow, oxidative stress and defective fatty acid metabolism in diabetes may lead to impaired nerve perfusion may contribute to development of peripheral neuropathy. Untreated diabetic rats had impaired sciatic motor and saphenous sensory nerve conduction velocity [NCV], reduced endoneural blood flow and increased serum triglycerides, cholesterol, plasma factor and vonwillebr and factor. Treatment with either ALA/EPO effectively corrected the defect in NCV and endoneural blood flow.α-lipoic acid was associated with marked and statistically significant decrease in fibrinogen, factor 7, vonwillebrand factor, triglycerides. In contrast EPO is associated with significant increase in fibrinogen, factor 7, vonwillebrand factor and decrease in HDL. Blood glucose levels and hematocrit were not significantly altered by treatment. These data suggest that although both ALA and EPO improve blood flow and nerve function, their actions on vascular factors differ. The marked effects of ALA in lowering lipid and hemostatic risk factor for CVS disease indicate potential antithrombotic and anti-atherosclerotic action that could be benefit in human diabetes. Reduced nerve conduction in experimental diabetes can be prevented by evening prime rose oil, which is rich in γ-linolenic acid. Natural GLA rich oils have a complex composition. Their GLA containing triglycerides configuration may significantly absorption, bioavailability and biological activity. Stimulation of arachidonic acid synthesis from these oil could have potential deleterious effects on NCV in diabetic rates by

further elevating thromboxane A2 [TXA2] production to promote platelet aggregation and vasoconstriction, which may exacerbate nerve perfusion. Motor and sensory NCV defects can be corrected by GLA containing oils in diabetes rat the degree of amelioration was not directly predictable on the basis of GLA content alone. Saphenous NCV was more influencable than sural motor NCV to treatment with previous findings for aldose reductase inhibitor, anti and vasodilators suggesting a general treatment susceptibility, rather an effect specific to essential fatty acids. Garlic Oil And Melatonin treatment of diabetic rat with garlic oil[10mg/kgi. p] or melatonin[200mg/kgi.ps] for 15 days significantly increased plasma level of total thiol, ceruloplasmin activities, albumin. Lipid peroxidases, uric acid, blood glucose total lipid, triglyceride and cholesterol were decreased. Nitric oxide levels were decreased with melatonin treatment alone. In RBC lysate, glutathione-s- transferase [GST] activities were increased significantly in rates treated with garlic oil or melatonin. While lipid peroxidases were decreased significantly with melantonin and garlic oil treatment. Super oxidase dismutase [SOD] activities were increased significantly in liver and kidney after melantonin or garlic oil treatment. This result suggests that garlic oil or melantonin may effectively normalize the impaired antioxidant status in streptozotocin induced rats. The effects of these antioxidants may be useful in delaying the complicated effects of diabetes such as retinopathy, neuropathy and nephropathy due to imbalance between freeradicals and antioxidants. Moreover melatonin may be more powerful free radical scavenger than garlic oil. Diabetes mellitus has been shown to be a state of increased free radical production. Mechanism of action that contribute to the formation of free radical may include not only increased non enzymatic and auto oxidative glycosylation, but also metabolic stresses resulting from changes in energy metabolism. Melantonin scavenge free radical and prevent oxidative stress. It is a powerful antioxidant. Hygrophilia Erecta [23] Diabetic cystopathy manifested by an enlarged bladder is mainly caused by peripheral neuropathy. It is well established that diabetes mellitus induces dysfunction of lower urinary tract which occurs in 26.87%of cases. The first manifestations is usually the insidious onset of impaired bladder sensation due to autonomic neuropathy. If this continues, the inability to perceive distention of the bladder results in a large bladder. In addition, diabetic autonomic neuropathy may progress to a motor disturbance which affects the hypocontractile dextrusor muscle. The tropical plant, hypographilia erecta has been shown to contain some long fatty alcohols that demonstrate neurotropic activities on cultured neurons on from the cerebral cortex. The c-20 alcohol n- hexacosanol was found to increase neurite extension as well as biochemical differentiation of neuron directly. It was also reported that peripheral administration of this compound prevented neuronal death in the brains of rats. These findings are particularly interesting because long chain fatty alcohol have been shown to be synthesized by rat brain as well as sciatic nerve during development. Brown Algae [24] among marine algae, brown algae have been extensively studied for their antidiabetic activities. Majority of the investigations on phlorotannins derived from brown algae exhibit their various antidiabetic activities such as α-glucosidase inhibitor,α amylase effect, glucose uptake effect in skeletal muscle, protein tyrosine phosphatase 1B[PTP1B] enzyme inhibitor. Improvement of insulin sensitivity in type2 diabetes and protection against diabetic complications. Tetrafucol A, a fucol type phlorotannin found in the brown algae Ascophyllum nodosum is responsible for anti-diabetic activity. Rutin [25] is also called rutoside, quercetin-3- O-rutinoside and sophorn, is the glycoside between the flavanol quercetin and the disaccharide rutinose. Rutin an aldose reductase inhibitor (ARI), and was found to show a protective effect aganist diabetic neuropathy by its metal chelating property. It will chelate the metal that causes Fenton reaction.

Conclusion [25, 26]

Diabetes mellitus is a chronic metabolic disorder of impaired carbohydrate, fat and protein metabolism. Diabetes mellitus can leads to various complications such as diabetic neuropathy, diabetic retinopathy etc. Allopathic medicines are not effective in treating the disease, leading to various adverse effects. Various alternative therapies for diabetic neuropathy including yoga, anodyne therapy, stem cell therapy, non -viral gene therapy, decompression surgery, low intensity laser treatment, gene therapy, aromatherapy, acupuncture, homeopathy etc are also there. But theses treatment has its own adverse effects. Hence medicinal plants are the best alternative treatment for the treatment of diabetes mellitus and its associated complication neuropathy. The plant species are proved their efficacy. Limiting diabetes mellitus without any side effect is a challenge still to the medical system. In recent years herbs have become a subject of interest because of their effect of beneficial effect on human health. This review article explored the role of herbs in the treatment of diabetes and its associated complications diabetic neuropathy, diabetic retinopathy In near future herbal plants will play a crucial role in modern system of medicine for the treatment of diabetes mellitus and its associated complications like diabetic neuropathy.

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