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ANTI-DIABETIC PROFILE OF HERBAL DRUGS: A REVIEW

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ABSTRACT

Diabetes mellitus is a common and very prevalent disease affecting the citizens of both developed and developing countries. It is estimated that 25% of the world population is affected by this disease. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin. In the present review we discussed about Herbal medicinal plants for the treatment of Diabetes mellitus. Herbs are used to manage Type 1 and Type II diabetes and their complications. This study may be useful to the health professionals, scientists and scholars working in the field of pharmacology and therapeutics to develop antidiabetic drugs.

1. INTRODUCTION

The use of herbal drugs is probably as old as the beginning of human beings on this earth. Almost one fourth drugs used in the pharmaceutical industries are derived from the herbal sources. The search for new chemical constituents from many herbal sources has been rapidly escalating in recent few decades. Many plant derived products are used in health supplements[1].

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia (high blood glucose) and other signs, as distinct from a single illness or condition. It is a chronic metabolic disease with inability to maintain blood glucose concentrations within physiological limits. It develops when the pancreas does not produce enough insulin or when the body cannot utilize the produced insulin effectively in the body.

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The World Health Organization (WHO) recognizes the three types of diabetes: type 1, type 2 and gestational diabetes, which have comparable signs, symptoms and consequences, but different causes and population distributions. Ultimately, all forms are due to the β cells of the pancreas being unable to produce sufficient insulin to prevent hyperglycemia.[3] Type 1 is usually due to autoimmune destruction of the pancreatic β cells which produce insulin. Type 2 diabetes is characterized by tissue-wise insulin resistance and varies widely; it sometimes progresses to loss of β cell function. Gestational diabetes result from insulin resistance (the hormones of pregnancy cause insulin resistance in those women who are genetically predisposed to developing this condition) is similar to type 2 diabetes.[2]

The latest WHO estimate shows that diabetes death will double between 2005 to 2030 and this number is predicted to increase by 5.5% every year, reaching 366 million people in 2030.[4]

2. Type 1 diabetes mellitus (T1DM):

It is also known as insulin-dependent diabetes mellitus (IDDM), childhood diabetes or juvenile diabetes (because it mainly affect children), is characterized by the loss of insulin producing β cells of the islets of Langerhans of the pancreas leading to a deficiency in insulin production. It should be noted that there is no known preventative measure that can be taken against type 1 diabetes. Most people affected by type 1 diabetes are otherwise healthy and of a healthy weight when onset occurs. The main cause of β cell loss leading to type 1 diabetes is a T-cell mediated autoimmune attack.[3] Deficiency of insulin results in altered carbohydrate and lipid metabolism which leads to ketosis and diabetic ketoacidosis, coma or death. Currently, type 1 diabetes can be treated only with insulin, with careful monitoring of blood glucose levels using blood testing monitors. Treatment of Type 1 diabetes mellitus must be continued throughout life.[5]

2.1. Type 2 diabetes mellitus (T2DM):

Synonymously called adult-onset diabetes, maturity-onset diabetes in young (MODY), or non-insulin-dependent diabetes mellitus (NIDDM); is due to a combination of defective insulin secretion and insulin resistance or reduced insulin sensitivity (defective responsiveness of tissues to insulin), which almost certainly involves the insulin receptor in cell membranes. Type 2 diabetes mellitus is one of the most chronic metabolic disorder associated with co-morbidities such as obesity, hypertension, hyperlipidemia and cardiovascular disease, which, taken together, comprise the 'metabolic syndrome'. Type 2 diabetes mellitus is characterized by postprandial hyperglycemia that results from defects in both insulin action and secretion. Its chronic complications include vision damage due to retinopathy, renal failure due to nephropathy, loss of sensation or pain due to neuropathy, and accelerated atherosclerosis, which results in blindness, end-stage renal disease, amputations, and premature cardiovascular mortality. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes.[6]

2.2. Pathogenesis of type 2 diabetes:

β-cell dysfunction and insulin resistance type 2 diabetes is usually the product of two distinct abnormalities viz. abnormal β-cell function and decreased insulin sensitivity. It appears that type 2 diabetes is primarily a genetic disease, based on its strong familial association and high concordance rates in identical twins[7]. However, no single gene has been identified that is common to a general population of type 2 diabetic patients, leading to the conclusion that this must be a polygenic disease[8-10].

Most of the type 2 diabetic patients are obese, who generally have resistance to the actions of insulin on liver, muscle and fat tissues (the major targets for the beneficial effects of insulin). An environmental influence also plays a major role by enhancing the phenotypic expression of genes that place individuals at risk for diabetes. This is becoming increasingly apparent as witnessed by the recent epidemic proportions of new-onset type 2 diabetes in cultures such as American Indian, African American, Latino, and Alaskan American. The obesity, insufficient physical activity, and excessive carbohydrate intake is an immense reason for diabetes. These clinical essentials point to the conclusion that the preliminary lesion in type 2 diabetes almost certainly involves hereditarily gritty reduction of intrinsic β-cell function, which is thus unable to passably meet the challenge of states of insulin resistance, such as obesity. As a result, the β-cell is frequently called upon to generate insulin because of uncertain hyperglycemia, and this stress progressively causes β-cell descent and accelerated apoptosis[11]. Both β-cell dysfunction and insulin confrontation works in concert to cause further descent of insulin secretion and increase insulin resistance. Nonetheless, it is interesting to consider that not all lean type 2 diabetic patients are insulin resistant, and that patients with cystic fibrosis and type 2 diabetes are characteristically insulin sensitive.[12]

2.3. Glucolipotoxicity in the β-cell and oxidative Stress:

The general findings of prominent glucose and lipid levels in the blood of diabetic patients led to glucose toxicity[13] and lipotoxicity.[14] Relatively more information has been published about biochemical pathways through which elevated glucose concentrations can generate excessive levels of reactive oxygen species (ROS).[15] These include glycolysis and oxidative phosphorylation; methylglyoxal formation and glycation; enediol and α-ketoaldehyde formation (glucoxidation); diacylglycerol formation and protein kinase C activation; glucosamine formation and hexosamine metablolism; and sorbitol metabolism. Conceptually, as β-cells are exposed to high glucose concentrations for increasingly prolonged periods of time, glucose saturates the normal route of glycolysis and increasingly is shunted to alternate pathways, such that reactive oxygen species are generated from distinct metabolic processes within and outside the mitochondria. The results also indicate that extreme levels of palmitate are allied with anomalous islet function, which leads to extreme lipid esterification that can produce ceramide, thereby escalating oxidative stress.[14-16] It seems unlikely that circulating lipid level of triglyceride or cholesterol, would be accountable for destructive islet tissue and excessive circulating glucose levels lead to accelerated de novo synthesis of islet lipid. Its ability to drive synthesis of malonyl CoA, glucose contributes to lipotoxicity which inhibits β-oxidation of free fatty acids. This in turn shunts free fatty acids towards esterification pathways, thereby forming triglyceride, ceramide and other esterification products[17, 18].

Lipotoxicity requires concomitant hyperglycemia to damage islet function, whereas glucose toxicity can exert harmful effects on the islet in the absence of elevated circulating triglyceride.[19]

The chronic hyperglycemia can cause aggravation β-cell function during decreased protein expression of two important transcription factors: Pdx-1 (Pancreatic and duodenal homeobox-1) and MafA (Mammalian homologue of avian).[15] Both proteins are critical for normal insulin gene expression, as their absence or mutation of their DNA binding sites on the insulin promoter leads to decreased mRNA levels, content and secretion of insulin[20.]

2.4. Glucolipotoxicity in non-β cells, insulin resistance and oxidative stress:

Insulin resistance convoy the progress of pregnancy, obesity, excess growth hormone and glucocorticoid levels, and lack of exercise.

Oxidative Stress play a significant role in insulin resistance and in the cellular damage of tissues that leads to the late complications of diabetes. Abnormal levels of free fatty acids, tumour necrosis factor-α, leptin and resistin are frequently found in obese individuals and are prominently mentioned as potential mediators of insulin resistance. Free fatty acids have been reported to impair insulin action through oxidative stress induced activation of nuclear factor-kβ. Secondary complications of diabetes involve microvascular and macrovascular changes that lead to retinopathy, nephropathy, neuropathy and damage to critical blood vessels, such as the coronary arteries.

Table 1. Allopathic Treatment: Approaches to Drug therapy in Diabetes [23]

S.No.	*Drug used*		
1	Sulfonylureas	First generation (i)Tolbutamide (ii)Acetohexamide (iii)Chlorpropamide (iv) Tolazamide	Second generation (i)Glimepiride (ii)Glyburide(glibenclamide) (iii)Glipizide (iv) Gliclazide
2	Other insulin secretagogues (i) Repaglinide (ii) Nateglinide		
3	Biguanides (i) Metformin		
4	Thiazolidinediones (i)Pioglitazone (ii)Trovaglitazone (iii) Rosiglitazone		
5	Alpha-glucosidase inhibitors (i)Acarbose (ii) Miglitol		
6	Dipeptidyl peptidase-4 (DPP-4) inhibitors (i)Sitagliptin (ii) Saxagliptin Glucagon-like-polypeptide 1 (GLP-1) analogues (incretin mimetics) (i)Exenatide (ii)Liraglutide (iii) Taspoglatide Amylin analogue (i) Pramlintide		

Stress-activated signaling pathways that might play a role in these phenomena are those involving protein kinase C, nuclear factor-kβ, p38 mitogen-activated protein kinase, advanced glycosylation end-products and their receptors and amino-terminal JUN kinases.[21] Antioxidant agents that have been reported to diminish insulin resistance, are lipoic acid, NAC, aminoguanidine, vitamin C, vitamin E, resveratrol, silymarin and curcumin.

Table 2. Herbs having Anti-diabetic potential

No.	*Biological Name*	*Common Name*	*Parts Used*	*Model*
1.	*Acacia Arabica*[25] (Leguminosae)	Babul	Seeds	Alloxanized rats
2.	*Aegle marmelos*[26] (Rutaceae)	Bael	Leaves	STZ diabetic rats
3.	*Allium cepa*[27] (Liliaceae)	Piyaj	Bulbs	STZ diabetic rats
4.	*Areca catechu*[28] (Arecaceae)	Supari	Nuts	Alloxanized rabbits
5.	*Azadirachta indica*[29] (Meliaceae)	Neem	Leaves	STZ diabetic rats
6.	*Aerva lanata*[30] (Amaranthaceae)	Kapuri jadi	Shoots	Alloxanized rats
7.	*Andrographis paniculata*[31] (Acanthaceae)	Kalmegh	Leaves	Normal and STZ diabetic rats
8.	*Artemisia pallens*[32](Compositae)	Davana	Leaves	Alloxanized rats
9.	*Annona squamosa*[33] (Annonaceae)	Seethaphal	Leaves	STZ diabetic rats, alloxanized rabbits
10.	*Anacardium occidentale*[34] (Anacardiaceae)	Kaju	Leaves	Normal and alloxanized rabbits
11.	*Biophytum sensitivum*[35] (Oxalidaceae)	Lajjalu	Leaves	Alloxanized male rabbits
12.	*Beta vulgaris*[36] (Chenopodiaceae)	Chukkander	Roots	Normal rats
13.	*Boerhavia diffusa*[37] (Nyctaginaceae)	Punarnava	Leaves	Alloxanized rats
14.	*Cassia auriculata*[38] (Leguminosae)	Tarwar	Flower	STZ diabetic rats
15.	*Caesalpinia bonducella*[39] (Caesalpiniaceae)	Karanju	Seeds	STZ diabetic rats
16.	*Catharanthus roseus*[40] (Apocynaceae)	Sadabahar	Leaves	STZ diabetic rats
17.	*Citrullus colocynthis*[41] (Cucurbitaceae)	Badi Indrayan	Seeds	Normal and STZ- diabetic rats
18.	*Coccinia indica*[42] (Cucurbitaceae)	Kanturi	Leaves	Alloxanized dogs
19.	*Cajanus cajan*[43] (Fabaceae)	Tuvar	Seeds	Normal and alloxanized mice
20.	*Eugenia jambolana*[44] (Myrtaceae)	Jamun	Fruit	Normal and STZ- diabetic rats
21.	*Ficus bengalensis*[45] (Moraceae)	Bur	Bark	Normal and alloxanized rabbits
22.	*Hibiscus rosa-sinesis*[46] (Malvaceae)	Gudhal	Leaf	STZ diabetic rats
23.	*Mangifera indica*[47] (Anacardiaceae)	Aam	Leaf	STZ-diabetic rats
24.	*Momordica cymbalaria*[48] (Cucurbitaceae)	Kadavanchi	Fruit	Alloxanized rats
25.	*Morus alba*[49] (Moraceae)	Shetut	Leaves	STZ diabetic mice
26.	*Musa sapientum*[50] (Musaceae)	Kela	Flowers	Alloxanized rats
27.	*Memecylon umbellatum*[51] (Melastomataceae)	Anjani	Leaves	Normal and alloxanized rats
28.	*Mucuna pruriens*[52] (Leguminosae)	Kiwach	Seeds	Alloxanized rats
29.	*Nelumbo nucifera*[53] (Nelumbonaceae)	Kamal	Rhizome	STZ diabetic mice
30.	*Ocimum sanctum*[54] (Lamiaceae)	Tulsi	Leaves	Normal and STZ- diabetic rats
31.	*Picrorrhiza kurroa*[55] (Scrophulariaceae)	Kutki	Roots	Alloxanized rats
32.	*Salacia Oblonga*[56] (Celastaceae)	Ponkoranti	Root bark	STZ-induced diabetic rats
33.	*Swertia chirayita*[57] (Gentianaceae)	Chirata	Aerial part	STZ-induced albino rats
34.	*Tinospora cordifolia*[58] (Menispermaceae)	Guduci	Roots	Alloxanized rats
35.	*Zingiber officinale*[59] (Zingiberaceae)	Adrak	Rhizome	STZ-diabetic rats
36.	*Terminalia catappa*[60] (Combretaceae)	Deshibadam	Fruit	Alloxanized rats
37	*Semecarpus* anacardium[6] (Anacardeaceae)	Bhallaatak	Aerial part	Alloxanized rats

Vascular endothelial growth factor has been proposed as an initiator of diabetic complications; whereas antioxidants have been reported to inhibit advanced glycosylation end-product-induced expression of vascular endothelial growth factor.[22]

2.5. Ayurvedic Treatment

In Ayurveda, plant parts of different species have been used against various diseases since time immemorial. The ancient man used herbs as therapeutic agents and medicaments, which they were able to procure easily. The nature has provided abundant plant wealth for all living creatures, which possess medicinal virtues.

Many traditional plant treatments for diabetes are used throughout the world. Plant drugs and herbal formulation are frequently considered to be less toxic and free from side effects than synthetic one. Based on the WHO recommendations hypoglycemic agents of plant origin used in conventional medication are important.[24]

3. CONCLUSION

In the present review we discussed about Herbal medicinal plants for the treatment of Diabetes mellitus. Herbs are used to manage Type 1 and Type II diabetes and their complications. For this, therapies developed along the principles of western medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. This study may be useful to the health professionals, scientists and scholars working in the field of pharmacology and therapeutics to develop antidiabetic drugs.

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