

Diabetes: Symptoms, Cause and Potential Natural Therapeutic Methods

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Abstract Diabetes mellitus (DM) commonly referred as diabetes is a complex, heterogeneous disorder characterized by high blood glucose level. Insulin insufficiency or ineffective insulin termed as insulin resistance contributes to diabetes etiology. There are two major forms of DM termed as type-1 diabetes and type-2 diabetes. Type-1 diabetes is an autoimmune disease resulting in destruction of pancreatic cell leading to severe lack of insulin. Whereas, type-2 diabetes develop due to inefficient insulin utilization referred as insulin resistance or insufficient quantity of insulin production. Diabetes has become a global disease and in 2014 WHO has reported 9% of adults (18 years and above) had diabetes. The above trend is expected to increase in forthcoming years due to sedentary lifestyle, unhealthy diet and excessive body weight. Insulin signaling pathway is the key pathway involved in regulating blood glucose level. There are several factors reported to alter insulin secretion as well as insulin signaling pathway resulting in etiology and progression of diabetes. Diabetes treatment aims at controlling blood glucose level. There are various kinds of chemical drug and herbal/natural products being used to effectively control blood glucose level. Composition, dosage and mode of action of chemical drugs are well established. However, the mode of action of traditional and herbal medications, which are used widely by 90% of the population in developing countries for primary healthcare, is still poorly investigated. Around 800 plants have been reported worldwide which have anti-diabetic potential. This review explores and gives the insight on the insulin signaling pathway and other known factors which modulates diabetes. It also collates the potential of various anti-diabetic herbal/phytochemical medications which have been scientifically investigated for their anti-diabetic virtue and mode of action.

Keywords Diabetes, Insulin Signaling, Obesity, Herbal Medications

1. Introduction

Diabetes mellitus (DM) commonly referred as diabetes is characterized by high blood glucose. It is a metabolic disorder caused due to insufficient or ineffective insulin [1]. Insulin is a hormone produced by the pancreas in the islets of langerhans which regulates the blood glucose level. In a diabetic person glucose is not absorbed properly by target cells, resulting in excessive blood glucose level (a condition known as hyperglycemia) in circulation. Hyperglycemia for prolonged period results in damage to nerves, blood vessels and body organs; ultimately it may lead to life-threatening complications. WHO has reported that, in 1995 around 4% of the world's population was affected by diabetes and it is expected to increase up to 5.4% by the year 2025 [2]. It is a chronic disorder without any permanent cure. Only timely diagnosis, proper management and treatment of the disease can aid in leading a normal healthy life.

Type-1 and type-2 are the two major forms of diabetes. Type-1 diabetes also termed as insulin-dependent diabetes is an autoimmune disorder [3]. It results in the destruction of most of the beta cells in the islets of langerhans (Pancreas) resulting in severe lack of insulin [3]. Approximately 10% of the total diabetic population is reported to be affected by type-1 diabetes and rest 90% are type-2 cases [4]. Type-1 diabetes is often referred as juvenile diabetes as it accounts for about 10% of diabetic cases in youth below the age of 25. Some of the symptoms of type-1 diabetes are: weight loss, frequent urination, fatigue, increased thirst, blurred vision [3]. Treatment of type-1 diabetes involves regular blood glucose monitoring and insulin administration, strict diet regime and exercise [5].

The type-2 diabetes is also known as non-insulin-dependent diabetes [6, 7]. In type-2 diabetes

body is not able to effectively utilize insulin produced by pancreas, which is termed as insulin resistance, or the pancreas do not produce sufficient quantity of insulin [6, 7]. This type of diabetes has late onset and appears usually after the age of 40. Overweight or obesity as well as genetic factors have been reported to be associated with onset of type-2 diabetes [7]. Some of the symptoms of type-2 diabetes are frequent infections, blurred vision, delayed healing of cuts/wounds, tingling/numbness in the extremities, recurring skin/gum or bladder infections [7] Treatment of type-2 diabetes involve keeping blood glucose level in control by healthy diet, exercise and making lifestyle changes as required.

Several studies have been carried out to investigate the cause of diabetes. It has been found that diabetes is a complex, heterogeneous disorder and is modulated by several factors such as hormones, genetics, obesity, ethnicity, age, molecular factors, biochemical factors and insulin signaling to list a few (Figure 1). Therapeutic strategy aimed by most of the anti-diabetic formulations/medicines prescribed is to check or lower the blood glucose. Apart from conventional medicines prescribed some patients use complementary or alternative therapies for treating diabetes. Many phytochemicals or herbal formulations have been reported to be quite effective in control and management of diabetes though clear insight on their mode of action is unavailable. This review gives the insight on all the probable factors modulating diabetes and highlights some of the medicinal plants which are widely used and have been well explored for their anti-diabetic effects.

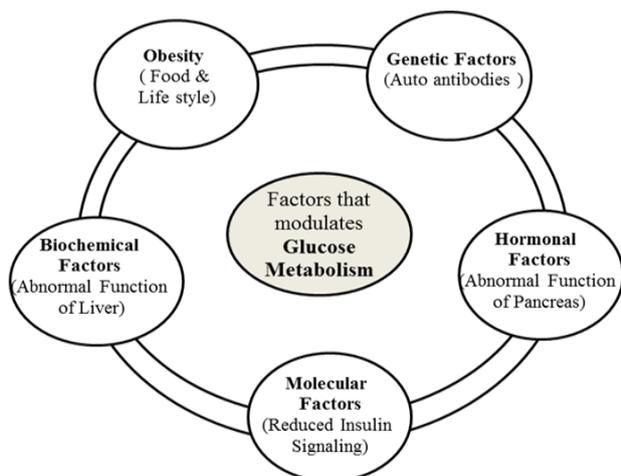


Figure 1. Summary of the factors modulating Glucose metabolism.

2. Insulin Signaling Cascade-An Overview

Cytokines such as tumor necrosis factor- α (TNF α), interleukin-6 (IL-6) and leptin activate the insulin signaling pathways [8]. There are three critical nodes or potential cross

talk junctures reported for the insulin pathway 1) insulin receptor (IR) and insulin receptor substrate proteins (IRS proteins). The former (IR) phosphorylates the later (IRS) in presence of insulin. 2) The phosphatidylinositol 3-kinase (PI3K). IRS interacts with PI3K and generate phosphatidylinositol-3, 4, 5-triphosphate (PIP3) 3) AKT/protein kinase B (PKB) [8].

Insulin binding to the insulin receptor (IR) activates the receptor's tyrosine kinase activity. IR is a heterotetrameric complex comprising of two "α" subunits and two "β" subunits linked together by disulfide bond [9]. Insulin binds to the "α" subunits, and activates "β" subunit by autophosphorylating its tyrosine residues. The β-subunit of IR has been reported to possess 13 tyrosine phosphorylation sites. Phosphorylated IR acts as docking site for adaptors like insulin receptor substrates (IRS1, IRS2, IRS3 and IRS4) and Shc. IRS1 and IRS2 are the key IRS targets and have great affinity for IR due to presence of pleckstrin-homology domains (PH domains) and phosphotyrosine-binding domains (PTB) domains [10]. IRS1 and IRS2 are involved in the PI3K/Akt signaling pathway which regulates glucose metabolism [10]. On the other hand Shc binding triggers the Ras-mitogen-activated protein kinase (MAPK) pathway, regulating in cell growth and differentiation [11, 12].

Phosphorylation of IRS1 and IRS2 creates docking site for SRC homology 2 (SH2) domains of the p85 regulatory subunit of PI3K [10]. The p110 catalytic subunit of PI3-kinase, phosphorylates phosphatidylinositol (4, 5) bisphosphate [PtdIns(4,5)P₂] forming Ptd(3,4,5)P₃ [8]. 3-phosphoinositide-dependent protein kinase 1 (PDK1) binds PIP3 through its PH domain and activates AKT (also known as protein kinase B/PKB) and atypical protein kinase Cs (aPKCs) by phosphorylation [8, 11]. PDK1 has been reported to only partially activate AKT/PKB and aPKC, whereas the full activation takes place by second phosphorylation event which is catalysed possibly by mTORC2 (mammalian target of rapamycin (mTOR) complex) [8, 11]. AKT/PKB activation regulates many pathways like glycogen synthesis, gluconeogenesis, glycogenolysis and glucose transport [8].

Activated AKT/PKB inactivates glucose synthase kinase-3 (GSK-3) by phosphorylation which in turn prevents it from carrying out inhibitory phosphorylation of glycogen synthase (GS) thus promoting glycogen synthesis [13, 14]. Activated AKT/PKB also activates protein phosphatase-1 (PP1) which activates glycogen synthase by dephosphorylation [13, 14]. Activated AKT/PKB also promote glucose uptake by translocating the glucose transporter GLUT-4 at the plasma membrane from their intracellular pool [15, 16]. Inhibitory phosphorylation of RabGTPase activating protein AS160 (for AKT substrate of 160 kDa) promotes GLUT-4 translocation pathway [15, 16]. Activated AKT/PKB inactivates FOXO1 by phosphorylation, which inhibits gluconeogenesis and promotes adipogenesis [17, 18]. Alteration and defects in the critical node signalling has been reported to result in diabetes and insulin resistance.

3. Factors Modulating Diabetes

Hormonal Factors

Two key hormones - insulin and glucagon regulate the blood glucose levels within the permissible limits. The islets of langerhans are the cluster of pancreatic cells which produce insulin and glucagons [19, 20]. Increased blood glucose levels (hyperglycemia) trigger beta cells of islets of langerhans to secrete insulin, which enhances glucose uptake by the cells. Inside the cell, the glucose is either converted into energy and used by the cell, or is converted to glycogen and stored mainly in the liver and skeletal muscles, or is used for the production of fats. Low blood glucose level or hypoglycemic condition triggers alpha cells of islets of langerhans to produce glucagon [19, 20]. Glucagon stimulates the breakdown of glycogen to glucose, which is then released into the bloodstream [19, 20] (Figure 2).

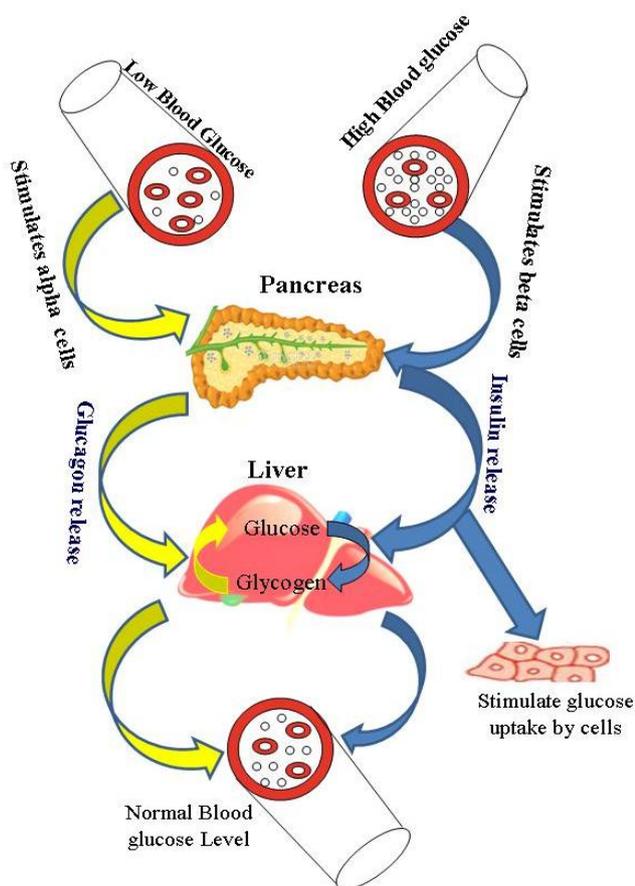


Figure 2. Role of insulin and glucagon in regulating blood glucose levels.

Genetic Factor

The quest to find why certain individuals are more prone to diabetes than others resulted in identification of genetic factors that modulate diabetes. Involvement of multiple genes as well as environmental factors contributes to the development of the both type of diabetes. First clue about inheritability of type-1 diabetes came from the finding that first degree relatives are at higher risks for developing type-1

diabetes [21]. Similarly monozygotic twins have been reported to have 45% concordance rate for type-1 diabetes [22]. It has been reported that 20 genetic locus have been associated with susceptibility to type-1 diabetes [23]. As type-1 diabetes is an autoimmune disorder genes in the human leukocyte antigen (HLA) region of chromosome 6 have been reported to be strongly associated with type-1 diabetes susceptibility [24]. HLA class II genes also referred as IDDM1 (insulin dependent diabetes mellitus locus 1) contribute to 40–50% risk for inheriting type-1 diabetes [25]. HLA-DQA1, DQB1 and DRB1 alleles of HLA have been primarily reported to be involved in type-1 diabetes associated risk [26, 27]. Insulin (INS) gene has been reported as IDDM2. IDDM2 locus is positioned on chromosome 11p15.5 and is reported to be the VNTR region of INS gene [28, 29]. Other type-1 diabetes susceptibility locus IDDM3–IDDM18 has also been identified [23]. CTLA-4 (cytotoxic T lymphocyte-associated 4) gene present on chromosome 2q31-35 has been reported as another locus associated with type-1 diabetes. Along with type-1 diabetes CTL4 has been reported to be associated with many other autoimmune diseases. CTLA-4 is designated as IDDM12 locus for type-1 diabetes [30, 31].

In contrast to type-1 diabetes which is an autoimmune disorder, type-2 diabetes is due to insulin deficiency or insulin resistance. There is a strong genetic component reported for type-2 diabetes; first degree relative of type 2 diabetes patients are 3 times more prone to diabetes compared to individuals without any family history [32, 33]. Similarly, monozygotic twins have been reported to have higher concordance rate for type-2 diabetes compared to dizygotic twins [22]. Many candidate genes based on insulin secretion, action, function, and glucose metabolism have been proposed and investigated for their connection with type-2 diabetes. Some of the genes found associated with type-2 diabetes are PPAR γ , ABCC8, and CALPN10. PPAR γ (peroxisome proliferator-activated receptor- γ) gene is reported to be involved in adipocyte and lipid metabolism. PPAR γ gene (Pro) is associated with decreased insulin sensitivity and hence type-2 diabetes risk [34]. ABCC8 (ATP binding cassette, subfamily C, member 8) and UKCNJ11 genes together form ATP-sensitive potassium channel and is involved in modulating the release of insulin and glucagon. Both the genes are involved in development of type-2 diabetes [35]. CAPN10 (calpain 10) gene has also been reported with type-2 diabetes susceptibility [36].

Obesity

One of the prime driving forces associated with diabetes is obesity. Diabetes and obesity have been reported as the biggest challenge of 21st century. Obesity has been reported as both risk factor as well as accelerator for development of both type-1 and type-2 diabetes. In case of type-1 diabetes it has been reported that age of onset became earlier in the cases of obese kids [37]. It has been reported that genetic factor predisposes the kids for diabetes whereas obesity accelerates the age of occurrence [37]. In case of type-2

diabetes it has been reported that 80-90% cases are obese. Obesity has been reported to effect fatty acid metabolism, glucose metabolism and also results in development of insulin resistance [38]. Increase in upper body fat and abdominal girth has been reported to be associated with occurrence of type-2 diabetes as well as cardiovascular disease [39]. Some of the mechanisms hypothesized for linking obesity to type-2 diabetes are increased adipokines, TNF- α production, ectopic deposition of fat and mitochondrial dysfunction [40, 41].

Molecular and Biochemical Factors

There are several molecular and biochemical factors reported to be associated with diabetes etiology and pathogenesis. Alteration and dysregulation of critical nodes involved in insulin signaling results in insulin resistance as in type-2 diabetes. Some of the factors which when altered leads to impaired insulin signaling are: tyrosine dephosphorylation, serine/threonine phosphorylation, insulin receptor internalization [42]. Insulin interacts with IR and triggers insulin receptor autophosphorylation, which in turn activates IRS and catalyses the phosphorylation of cellular proteins such as members of the IRS family. IRS than activates PI3K/Akt signaling pathway which regulates glucose metabolism or Ras-MAPK pathway, regulating cell growth and differentiation [10-12]. All these pathways function in an orchestrated fashion to promote translocation of glucose transporter GLUT-4, inactivates GSK-3 [13-16].

Excess adipose tissue and its dysfunction have been reported to be associated with insulin resistance and type-2

diabetes [43]. Cytokine α which is produced by adipocytes have been reported to be associated with insulin resistance and type-2 diabetes [44]. PPAR gamma has been reported as transcriptional regulator of adipogenesis and TNF-alpha has been reported to regulate transcription, translation and turnover of PPAR gamma biosynthesis [45]. Similarly, free fatty acids PPARs have been reported to inhibit insulin signalling at steps like phosphorylation of IR and IRS proteins [46]. Elevation of IL-6 has also been reported to be associated with insulin resistance [47]. Role of mitochondrial dysfunction has also been illustrated in insulin resistance and type-2 diabetes [48]. Deregulation of biochemical pathways such as glycolysis, glycogenesis, gluconeogenesis, glycogenolysis, and other pathways involved in glucose metabolism are also associated with insulin resistance and diabetes.

4. Herbal Medications / Phytochemicals: As Potential Alternative Therapies to Cure Diabetes

Drugs which are prescribed routinely for diabetes mellitus act on controlling blood glucose levels either by enhancing insulin secretion or regulating glucose metabolism. In the patients with type-1 diabetes insulin administration is the most prescribed therapeutic method. Whereas, in case of type-2 diabetes, apart from insulin administration other treatment approaches are also adopted [49].

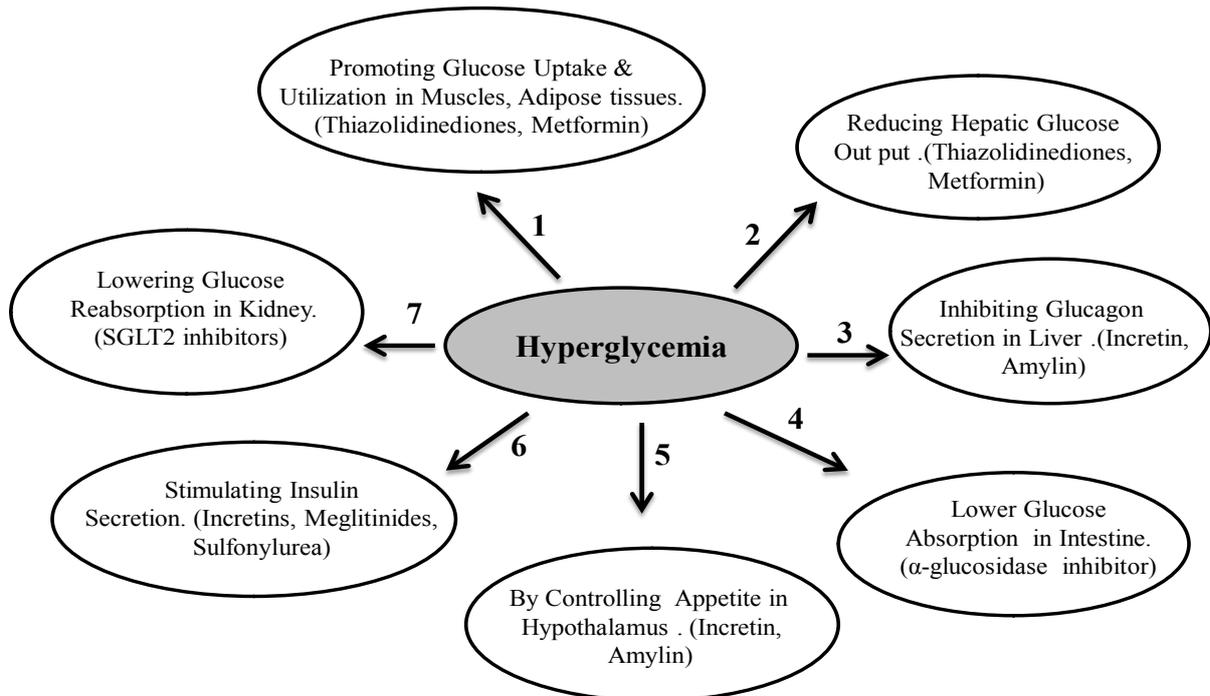


Figure 3. Mode of action of different drugs in treating hyperglycemic condition.

Drugs such as Biguanides are prescribed which prevent hepatic glucose production and improves insulin sensitivity in the body. Medications like Sulphonylureas act by increasing the pancreatic insulin production and improving the efficacy of insulin. Drugs like Thiazolidinediones act by improving insulin sensitivity. Other drugs like Alpha-glucosidase inhibitors act by retarding the rate of carbohydrate digestion in the small intestine and hence help in keeping blood glucose levels in control after the meals. Drugs like DPP-4 inhibitors and GLP-1 analogues act by stimulating insulin production and retarding glucagons production (Figure 3). Some of the side effects which have been reported for the chemical antidiabetic drugs are low blood glucose level (Sulphonylureas), stomach discomfort (Sulphonylureas, Alpha-glucosidase Inhibitors, DPP-4 Inhibitors, Biguanides), respiratory infection (DPP-4 Inhibitors), swelling or fluid retention, increased risk of congestive heart failure (Thiazolidinediones).

Use of traditional therapeutic methods like use of medicinal plants is the most widely used approach for primary health care across the globe as reported by WHO. As diabetes is a global disease which require lifelong monitoring and medication the anti-diabetic potential of several herbal plants has been experimentally tested and

proven. Many of these plant extracts are being effectively used either alone or in combination with conventional therapeutic methods for efficient treatment and control of diabetes. The high cost of chemical drugs, lifelong dependency, along with its side effects has made the alternative therapeutic medicines even more popular. Phytochemicals obtained from the medicinal plants aid in developing formulations for synthetic or semi-synthetic drugs. Mode of action of many antidiabetic plants has been studied and has been reported. Similar, to chemical drugs herbal medications also control blood glucose levels by the one of the following mechanisms like: increase insulin secretion, increase insulin sensitivity, inhibit gluconeogenesis and glycogenolysis in liver, stimulate glycogenesis, enhance uptake of glucose in adipose and skeletal muscles tissues, inhibiting absorption of glucose in intestine, improve glucose metabolism, reduce lipid per-oxidation, reduce oxidative stress (Figure 4) [50, 51]. Anti-diabetic action of some of the popular plants like *Momordica charantia*, *Trigonella foenum-graecum*, *Ocimum sanctum*, *Opuntia streptacantha*, *Silibum marianum*, *Azadirachta indica*, *Aegle marmelos*, *Aloe vera*, *Eugenia jambolana*, *Mangifera indica*, *Acacia Arabica*, *Ficus religiosa* is stated in the underlying sections.

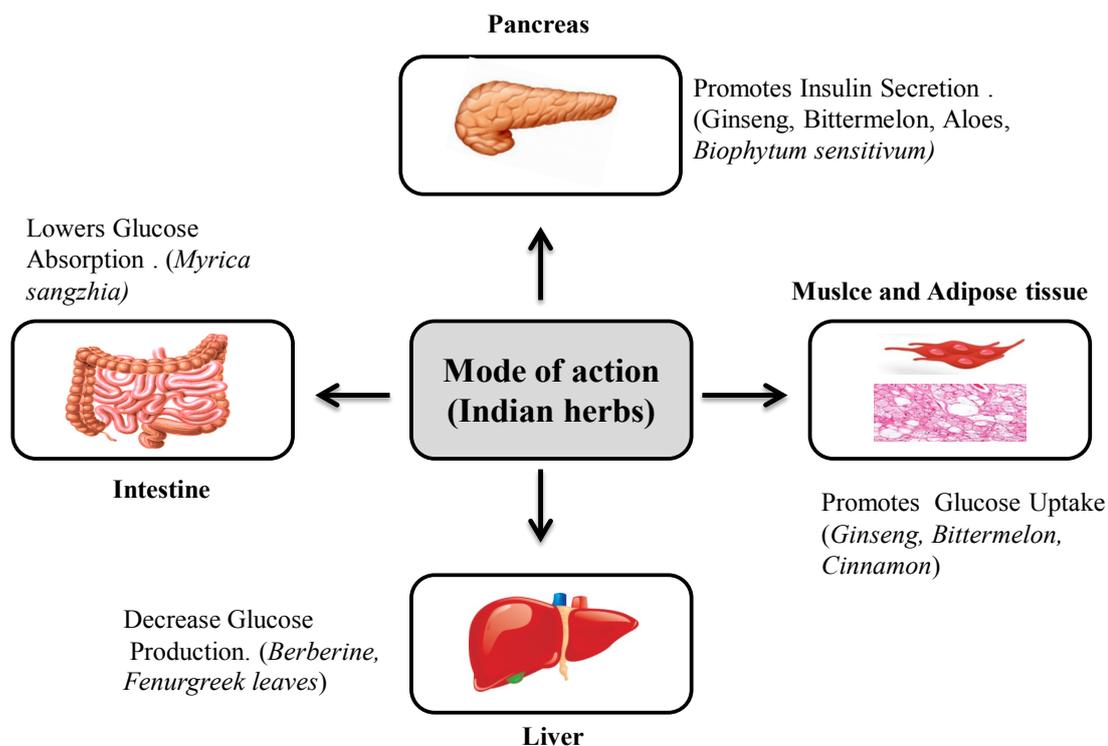


Figure 4. Mode of action of some of the anti-diabetic medicinal plants.

***Momordica charantia* (Bitter Gourd, Bitter Melon)
(Family: Cucurbitaceae)**

Momordica charantia commonly known as bitter gourd or bitter melon is a native of Indian subcontinent. It is widely known for its antidiabetic/hypoglycaemic effect and due to the same it is popularly termed as vegetable insulin. It is widely used for anti-diabetic therapy and testing of its anti-diabetic principle dates back to 1963 [52]. The extract obtained from the fruit has been reported to be homologous to pancreatic insulin and its hypoglycemic action has been well established based on clinical tests on humans as well as in animal models [53-57]. Several studies have been carried out to understand the mode of action of vegetable insulin. In a study done using diabetic rat models it has been reported that hypoglycemic effect of this plant is due to depression of the key gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and enhancing glucose oxidation by the shunt pathway by activating glucose-6-phosphate dehydrogenase (G6PDH) enzyme [58, 59]. The extract from *M. charantia* fruit has also been reported to exhibit both insulin secretory and insulin mimicking effect [60]. Acetone extract of *M. charantia* fruit has also been reported to promote recovery and regeneration of pancreatic islets in alloxan diabetic rats [61]. Extract of *M. charantia* has also been reported to inhibit activation of MAPKs and NF- κ B and this is the probable mechanism through which it exhibits protection to pancreatic β -cells [62]. Similarly, seed extract of *M. charantia* has also been reported to increase the expression of peroxisome proliferator-activated receptor- γ (PPAR- γ) and down-regulate the expression of NF- κ B [62, 63]. All the above lines of evidence thus stated support the antidiabetic potential of this plant.

***Trigonella foenum-graecum* (Fenugreek or Methi)
(Family: Leguminosae)**

Hypoglycemic, lowering lipid peroxidation and hypercholesterolaemic effect of fenugreek seeds has been widely studied and reported in different animal models [64-68]. Anti-diabetic active components present in fenugreek are galactomannan, 4-hydroxyisoleucin (4-OH-Ile), diosgenin and trigonelline. These substances have been reported to confer anti-diabetic properties by increasing insulin secretion (4-OH-Ile), decreasing insulin resistance (galactomannan), decreased glucose absorption in the intestine and promote recovery and regeneration of pancreatic beta cells (trigonelline) [69]. Seed extract powder of fenugreek has been reported to improve glucose homeostasis by improving the activities of the glycolytic and decreasing activities of gluconeogenic and lipogenic enzymes in liver of alloxan-induced diabetic wistar rats [70]. Fenugreek leaves have also been reported to show anti-diabetic action by regulating carbohydrate metabolism and reducing oxidative stress [71-73]. Seed extract of fenugreek has been reported to exhibit anti-hyperglycemic effect by stimulating insulin signaling pathway by promoting

phosphorylation of IR and IRS. In vitro analysis reported that hypoglycemic effect of fenugreek is due to GLUT4 translocation to plasma membrane [74]. Clinical trial with dietary supplementation of Fenugreek in prediabetes cases results in lower conversion to diabetes [75].

***Ocimum sanctum* (Sacred Basil or Tulsi) (Family: Lamiaceae)**

Ocimum sanctum also known as sacred basil is an herb widely used in traditional Indian ayurvedic practices. Leaf extract of the plant has been reported to exhibit hypoglycemic, hypolipidemic and antioxidant properties in animal model for diabetes [76-79]. The antidiabetic effect resulting in lowering of blood glucose, glycosylated hemoglobin, lipid peroxide, free fatty acids has been attributed due to its effect in stimulating insulin secretion [80, 81].

***Opuntia streptacantha* (Nopal or Prickly Pear) (Family: Cactaceae)**

Opuntia streptacantha belongs to the family Cactaceae and is commonly known as the prickly-pear. Traditionally Mexicans were using *Opuntia streptacantha* as antidiabetic medicine. Hypoglycemic properties of this plant have been experimentally demonstrated in various animal models [82, 83]. Administration of *Opuntia streptacantha* plant extract to diabetic patients has been reported to result in decreased blood glucose and insulin levels [84, 85]. The mechanism of action of this plant is still poorly understood.

***Silibum marianum* (Milk thistle) (Family: Asteraceae)**

Silibum marianum also known as milk thistle, belongs to family Asteraceae. Medicinal property of this plant is mainly due to the presence of flavonolignans silymarin. Silymarin consists of mainly silibin A, silibin B, taxifolin, isosilibin A, isosilibin B, silichristin A and sildianin. Various lines of research investigations have reported antioxidative as well as hepatoprotective effect of silymarin [86-89]. Efficacy of silymarin in treating diabetes has also been investigated extensively in last one decade. Hypoglycemic and anti-hyperglycaemic effect of silymarin on animal model for diabetes has been demonstrated [90]. Clinical trial of silymarin on type-2 diabetic patients for four months has reported to result in significant decrease in the levels of glycosylated hemoglobin (HbA(1)c), fasting blood glucose and total cholesterol [91]. Efficacy of silymarin has also been reported to be in inhibiting the progression of diabetic nephropathy in diabetic rats, it increases activity of glutathione peroxidase and catalase in renal tissues [92, 93]. Formation of human islet amyloid polypeptide deposits in pancreatic islets has been reported as one of the important causes for pathology and progression of type-2 diabetes [94-96]. Silibin has been reported to inhibit human islet amyloid polypeptide oligomerization in pancreatic cells thus it maintains pancreatic islets vitality [97]. Isosilybin A has been reported as Peroxisome proliferator-activated receptor

gamma (PPAR γ) agonist, PPAR γ is involved in regulating glucose and lipid metabolism [98].

***Azadirachta indica* (Neem) (Family: Meliaceae)**

Azadirachta indica named as neem or margosa is one of the most widely used plant in medicinal practices of ayurveda, unani and homoeopathic. Every single part of the plant which includes root, stem, bark, leaves, flower, fruit and seeds have been reported to have healing/medicinal properties. Some of the active constituents present in neem are nortriterpenoids, limonoids, diterpenoid, azadirachtin, nimbin, nimbidin, myricitin, salanin, nimbidol. Extract obtained from the plant has been reported to exhibit anti-inflammatory, anti-hyperglycaemic, anti-ulcer, anti-malarial, anti-fungal, anti-bacterial, anti-viral, anti-oxidant, anti-mutagenic properties. Extracts of neem seeds, leaves, bark and flowers have been reported to exhibit anti-diabetic effect. [99-103]

Extract of neem bark and flower when administered to streptozotocin-induced diabetic mice has been reported to result in decrease in blood glucose level, moreover neem flower is reported to exhibit to stronger activity [99]. Similar effect of *A. indica* seed oil has also been reported using alloxan induced diabetes in rabbits [100]. Administration of extracts of neem seed kernel and husk has been reported to show anti-oxidative effect in erythrocytes of diabetic rats [101]. It leads to increased activity of superoxide dismutase (SOD) and catalase (CAT), and it decreases lipid peroxidation. It also resulted in significant decrease in levels of serum creatine phosphokinase (CPK) in diabetic rats [101]. Nimbidol present in roots, and bark of the *A. indica* has been reported to exhibit α -glucosidase inhibitor property [102]. Anti-diabetic effects of active components present in neem are also investigated in terms of its binding to diabetes mellitus type-2 protein enzyme target phosphoenol-pyruvate carboxykinase (PEPCK).

3-Deacetyl-3-cinnamoyl-azadirachtin present in the neem leaf extract has been reported to exhibit perfect binding with PEPCK [103]. All these investigations thus report the power of *A. indica* as a potent anti-diabetic plant.

***Aegle marmelos* (Bengal Quince, Bel or Bilva) (Family: Rutaceae)**

Aegle marmelos commonly known as bengal quince, bel or bilva is quite extensively described and used in Indian ayurvedic medicinal practices. All the parts of the plant which includes fruit, leaf stem, root and flower have been reported to have medicinal properties for curing many ailments. Some of the active components of the plant are marmelosin, alloimperatorin, marmelide, marmin, umbelliferone, isoimperatorin, skimmin, marmesin, marmesininbeta-sitosterol. Extract of fruit, leaf and bark of the plant has been extensively studied and have been reported to exhibit hypoglycemic effect [104-106]. Umbelliferone β -D-galactopyranoside extracted from the stem bark of the plant has been reported to exhibit anti-diabetic, anti-oxidant and anti-hyperlipidemic effect on

the streptozotocin induced diabetic rat [104]. Leaf extract of *A. marmelos* has also been reported to show therapeutic effect in animal model of early alloxan induced diabetic nephropathy [105]. Diabetic animals treated with *A. marmelos* leaf extract showed significant decrease in the fasting blood glucose level, total cholesterol, blood urea, compared to the diabetic control group. Morphological derangements due to diabetic nephropathy were reversed in aegle treated animals other renal parameters like thiobarbituric acid reactive substance (TBARS) showed a distinctive decline and there was increase in the levels of renal reduced glutathione and catalase [105]. The fruit extract of *A. marmelos* has been reported to exhibit antidiabetic, antihyperlipidaemic and antioxidant properties in streptozotocin induced diabetic rat. Streptozotocin induced diabetic rat groups treated with *A. marmelos* fruit extract also exhibited improved pancreatic function and the damage caused to pancreatic islets by streptozotocin was also found to be reversed [106]. Clinical trials using *A. marmelos* extract in type 2 diabetes patients also supports its hypoglycemic and blood pressure lowering effect [107].

***Aloe vera* (Family: Asphodelaceae)**

Aloe vera also known as *Aloe barbadensis* is a shrubby, xerophytic, green colored succulent plant belonging to Asphodelaceae family. Succulent leaf of the Aloe plant produces clear jelly like substance known as aloe gel and just beneath the leaf skin a yellow colored fluid is present known as latex. Both aloe gel and latex are used for medicinal applications. Aloe gel is used in preparation of aloe juice. Anti-diabetic, anti-oxidative, hypoglycemic and anti-hyperlipidemic properties of aloe gel and juice has been extensively investigated both in diabetic animal models as well as in human subjects [108-110]. In a study group comprising of human diabetic patients oral administration of aloe juice has been reported to result in decrease in blood glucose level and triglyceride level [108]. *Aloe vera* gel has been reported to exhibit both hypoglycemic and hypolipidemic effects in a mouse model of non-insulin-dependent diabetes mellitus [109]. Antioxidant and antidiabetic properties of *Aloe vera* has also been reported in streptozotocin induced rat models for diabetes [110]. Use of aloe preparations has also been found to be effective in reverting fasting glucose level and glucose tolerance in human cases of prediabetes/metabolic syndrome [111, 112]. Oral intake as well as topical application of *Aloe vera* gel extract has been reported to improve the wound ulcer healing in diabetic foot ulcer animal model the healing effect was due to increased DNA and glycosaminoglycans (GAGs) [113]. All the above lines of evidence support the anti-diabetic potential of *Aloe vera*.

***Eugenia jambolana* (Indian Gooseberry, Jamun) (Family: Myrtaceae)**

Eugenia jambolana or *Syzygium cumini* commonly named as jamun or black plum, belongs to the family Myrtaceae. Seeds of this plant are being used for treatment of diabetes

from many decades [114]. Plant, seeds and fruits are rich in some of the compounds like anthocyanins, glucoside, ellagic acid, isoquercetin, kaemferol, myrecetin, jambosine, and jambolin or antimellin which confers anti-oxidant, anti-inflammatory, anti-microbial, and gastro-protective properties. Extract from the fruit pulp and seed of the plant has been experimented and has shown both hypoglycemic as well as hypolipidemic effect [114-118]. Active ingredient isolated by LH chromatography using ethanolic seed extract of *Eugenia jambolana* has been investigated for its antidiabetic property [116]. The isolated seed extract when injected into alloxan induced diabetic rabbits resulted in significant decrease in fasting blood glucose levels, glycosylated hemoglobin and it also significantly enhanced plasma insulin level. Decoction of kernels as well as lyophilized powder of kernels has been reported to exhibit similar hypoglycemic effect in diabetes animal model. [115].

Hypoglycemic effect of fruit pulp has also been demonstrated in streptozotocin induced diabetic rats [117]. Isolated pancreatic islets of langerhans, when incubated with the *E. jambolana* fruit extract results in triggering insulin secretion [117]. Insulin resistance in type-2 diabetes results in diabetic dyslipidemia [119]. Efficacy of seed kernel has also been examined for its anti-hyperlipidemic effect in streptozotocin induced diabetic rats [118]. Ethanolic extract of seed kernel when administered orally in diabetic rat resulted in restoring normal levels of cholesterol, phospholipids, triglycerides and free fatty acids in these animals compared to untreated group which had higher levels of these lipids in plasma [118].

Increased oxidative stress has been reported to be associated with patho-physiology of diabetes [120]. Diabetic rat models have been reported to exhibit several markers for oxidative stress like increased levels of vitamin-E, lipid peroxides decrease in vitamin-C, reduced glutathione [121]. Activity of pancreatic antioxidant enzymes is also reported to be deregulated in pancreatic tissue. All these oxidative effects have been normalized in diabetic rats administered with seed kernel extract of *E. jambolana* [121]. Clinical trials done using *E. jambolana* seed extract has been reported to show significant hypoglycemic activity in type-2 diabetes mellitus subjects [122]. *E. jambolana* thus has antioxidative, hypoglycemic and anti-hyperlipidemic properties.

***Mangifera indica* (Mango) (Family: Anacardiaceae)**

Mangifera indica or Mango plant belonging to the family Anacardiaceae has been extensively investigated for its anti-diabetic effect. Extract of mango leaves, bark, and mango peel as well as freeze dried mango has been reported for its hypoglycemic effect [123-127]. Active constituent found in all these extracts is Mangiferin which is a xanthone which are known for its potent antioxidant effect. Anti-diabetic activity of Mangiferin, obtained from *Mangifera indica* bark, was tested on diabetic rats which were induced diabetes by high-fat/high fructose diet and streptozotocin. Treatment of mangiferin resulted in hypoglycemic effect routed through enhancing insulin

sensitivity, altering lipid profile and restoring normal adipokine levels. The effect of mangiferin was also found comparable to standard insulin sensitizer, rosiglitazone. [123]

Anti-diabetic effect of mango peel powder has also been investigated in streptozotocin-induced rat model of diabetes [124]. Supplement of mango peel powder in diabetic rats has been reported to resulted in increased anti-oxidative activity, decreased lipid peroxidation, it also resulted in decreased urine sugar, fasting blood glucose, total cholesterol, triglycerides and increased levels of high density lipoprotein compared to control [124]. Effect of freeze-dried mango supplement for 12 weeks was investigated on anthropometrics, body composition, and biochemical parameters in a study group comprising of obese individuals. Mango supplement was reported to result in significantly reduce fasting blood glucose level in the experimental set [125]. It has also been reported that mangiferin protects against high fat diet induced metabolic syndromes by promoting carbohydrate utilization [126]. Thus several lines of research investigation report antidiabetic virtue of *Mangifera indica* due to presence of xanthone compound mangiferin. Mangiferin has been reported to result in increase insulin sensitivity by improving carbohydrate utilization and metabolism [127].

***Acacia arabica*: (Acacia, Babul, and Gum Arabica) (Family: Fabaceae)**

Seed powder of *Acacia arabica* has been reported to exhibit hypoglycemic effect in rabbits [128]. *Acacia arabica* bark extract has been reported to decreases serum glucose and regulate lipid metabolism in alloxan induced diabetic rats [129]. Similar results pertaining to induction of decrease in serum glucose, insulin resistance, total cholesterol, triglycerides, low density lipoprotein cholesterol, and malondialdehyde has been reported in another research group in streptozotocin-induced diabetic rats. [130].

***Ficus religiosa* (Sacred Fig) (Family: Moraceae)**

Ficus religiosa commonly known as pipal or sacred fig has been known as religious as well as medicinal tree in Indian culture. Parts of this plant have been used to cure a wide variety of ailments. Extract of its bark and roots have been reported to have hypoglycemic effect [131]. Administration of bark extract in diabetic rats resulted in significant decrease in the levels of serum triglyceride and total cholesterol, at the same time it also induced significant increase in serum insulin levels in diabetic rat model [131]. Oxidative stress resulting in increased levels of plasma malondialdehyde (MDA) has been reported to be associated with diabetes [132]. Along with hypoglycemic effect aqueous extract of *Ficus religiosa* is reported to inhibit malondialdehyde formation and exhibit anti-oxidative effect in streptozotocin induced type 2 diabetic rats [133]. Activated immunity and inflammation has been reported to be associated in the early stages of diabetes 2 pathogenesis [134]. Administration of aqueous extract of *F. religiosa* has been reported to also have anti-inflammatory in type 2

diabetic rats [135]. Oral fig-leaf decoction has been reported to result in lowering of insulin dose in type-I diabetic patients [136]

5. Conclusions

Diabetes mellitus has become a global disease and there is an ever increasing rate for diabetes worldwide due to sedentary lifestyle, unhealthy diet and excessive body weight. Insulin signaling pathway is the key pathway which regulates blood glucose level. There are various factors reported to alter insulin secretion as well as insulin signaling pathway thus resulting in etiology and progression of diabetes. Managing blood glucose levels by medication, diet and exercise is the key for diabetes management and control. Proper understanding of the different causes of the disease and its possible control will aid in decreasing the disease incidence and its better management and cure. This review gives the insight on all the probable factors which affect the insulin signaling pathway and cause diabetes. The potential of various anti-diabetic herbal/phytochemicals which are tested for its anti-diabetic efficacy have been also extensively illustrated. Understanding the disease and making recommended lifestyle changes along with incorporation of anti-diabetic plants as diet supplement will go a long way in preventing, delaying the onset and effective management of the diabetes.

Abbreviations

DM: Diabetes mellitus; IR: insulin receptor; IRS: insulin receptor substrate; PI3K: phosphatidylinositol 3-kinase; PKB: protein kinase B; MAPK: mitogen-activated protein kinase; TNF- α : tumor necrosis alpha; GSK-3: glucose synthase kinase 3; HLA: human leukocyte antigen; IDDM: insulin dependent diabetes mellitus locus; PPAR γ : peroxisome proliferator-activated receptor- γ ; GLUT-4: glucose transporter 4.

Acknowledgements

Anjali Awasthi, Nikhat Parween and Jitendra Kumar contributed equally to this work.

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