



A REVIEW ON MEDICATION OF DIABETES MELLITUS AND ANTIDIABETIC MEDICINAL PLANTS

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Abstract: Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to defect in insulin secretion, insulin action or both. The aim of the diabetes treatment is primarily to save life and alleviate symptoms and secondary to prevent long term diabetic complications and, by eliminating various risk factors. The conventional drugs developed along the principles of western medicine are often limited in efficacy, carry the risk of adverse effects and are often costly, especially for the developing world. The prevalence of diabetes mellitus continues to rise worldwide. With the increasing incidence of diabetes mellitus in rural populations throughout the world, the inability of current therapies to control all the metabolic defects of the disease and their pathological consequences, and the expense of modern therapy, there is a clear need for the development of alternative strategies for diabetes therapy. The mechanism of action of herbal antidiabetic could be; stimulation of insulin secretion from beta cells, reduction in insulin resistance, stimulation of glycogenesis and hepatic glycolysis, activation of PPAR γ , inhibition of β -galactosidase and α -glucosidase and inhibition of glucose absorption from small intestine. Therefore, this review summarizes the current different antidiabetic drugs and also provides an overview of several medicinal plants used traditionally in the treatment of diabetes mellitus.

Key words: Diabetes Mellitus; Current Antidiabetic Drugs; Antidiabetic Medicinal Plants; Mode Of Action.

INTRODUCTION

Diabetes mellitus is a global metabolic disorder of the metabolism of carbohydrates, fats, and lipids, which is characterized by a high fasting blood sugar, which caused serious endocrine disorder that causes millions of deaths worldwide^{1,2}. Over the last century human life style and food habits have drastically changed which lead to various chronic diseases. The disease is associated with reduced quality of life and increased risk factors for mortality and morbidity³.

The World Health Organization (WHO) estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000. It is estimated that the number will increase to over 366 million by 2030 and that large increases will occur in developing countries, especially in people aged between 45 and 64 years⁴. The reasons for this global rise are growth of aged population, increasing trends towards obesity, unhealthy diet, and sedentary lifestyle⁵. Diabetes is nearing epidemic proportions as a result of an increased number of elderly people and a greater prevalence of obesity and sedentary lifestyle in people in developed and developing countries⁶. WHO estimated that diabetes resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death⁷. The cost of health care associated with diabetes continues to grow and is a huge economic burden for afflicted patient sand countries. The total estimated cost of diagnosed diabetes in 2012 in USA is \$245 billion, including \$176 billion in direct medical costs and \$69 billion in reduced

productivity⁸. To bring a new drug to market, the median cost per drug was \$350 million, but for companies with more drugs approved, the cost per drug went up until it hit \$5.5 billion for companies that have brought to market between eight to 13 drugs over a decade to perform the pharmacological and toxicological testing required by current strict regulations of the U.S. Food and Drug administration⁹.

Diabetes Classification:

There are three major types of diabetes:

1. Type-I (Insulin dependent diabetes mellitus).
2. Type-II (Non-insulin dependent diabetes mellitus).
3. Gestational diabetes mellitus¹⁰.

Type -I or Insulin Dependent Diabetes Mellitus:

In insulin dependent diabetes mellitus, insulin is completely absent because the pancreas lacks cells or contains defective cells. This condition occurs in genetically susceptible individuals from an autoimmune response that selectively destroys pancreatic cells. Their life spans are drastically reduced up to one third as a result of degenerative complications like kidney dysfunction, nerve impairment, and cardiovascular complications as well as blindness¹¹. Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide¹².

Type-II or Non-insulin Dependent Diabetes Mellitus:

Non-insulin dependent diabetes mellitus is characterized by reduced insulin secretion in response

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to glucose levels and insulin resistance which leads to the inefficient absorption of glucose into the cell for energy. It is present in 90% of the diagnosed cases of diabetes and affects 18% of the population above 65 years of age, usually occurs in obese individuals¹⁰. It eventually suppresses the synthesis of insulin receptor (a plasma membrane bound glycoprotein). Insulin resistance and insulin deficiency are common in the average NIDDM patients¹³. Insulin resistance is the primary cause of NIDDM, however some researcher contend that insulin deficiency is the primary cause because a moderate degree of insulin resistance is not sufficient to cause NIDDM¹⁴. Most patients with the common form of NIDDM have both defects. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes¹⁵.

Gestational diabetes mellitus:

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, irrespective of the glycemic status after delivery¹⁶. Insulin resistance and inadequate insulin secretion founded to play a central role in the pathophysiology of GDM¹⁷. Gestational diabetic women have increased risk of type 2 diabetes mellitus (T2DM) and heart disease later in life¹⁸, and their offspring have greater incidence of perinatal complications and increased risk of obesity and diabetes in adulthood¹⁹. It usually disappears after the birth of child, and it affects 3-10% of pregnancies, depending on the population studied²⁰.

Diabetes due to other causes:

Genetic defect of β -cell function characterized by mutation in hepatocyte nuclear transcriptional factor (HNF) 4 α , Genetic defect in insulin action, endocrinopathies such as acromegaly, Cushing's syndrome and hyperthyroidism, drug induced such as nicotinic acid, protease inhibitor and glucocorticoids and infections such as congenital rubella and cytomegalovirus²¹.

Diabetic complications:

Diabetes mellitus is a chronic metabolic disease with life threatening complications. Diabetes mellitus also causes "microvascular" complications leading to the small blood vessels damage. Diabetic retinopathy, affects blood vessel formation in the retina of the eye, can lead to problems in vision like reduced vision, and potential blindness²². Diabetic nephropathy, the complication of diabetes on the kidneys can lead to drastic changes in the kidney tissue, loss of progressively larger amounts of protein in the urine, and gradually leading to chronic kidney disease requiring dialysis¹⁰. Diabetic neuropathy is a vascular disease effecting circulation of blood in the legs,

contributing to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that are difficult to treat and occasionally require amputation²³.

Medication of Diabetes Mellitus

Conventional Antidiabetic Drugs: The currently available antidiabetic drugs manage the blood glucose levels under normal range by supplementing insulin, improving insulin sensitivity, increasing insulin secretion from the pancreas, decreasing glucose absorption from the intestinal tract and/or glucose uptake by tissue cells²⁴. The aim of the treatment is primarily to save life and alleviate symptoms, secondary aims are to prevent long term diabetic complications and, by eliminating various risk factors, to increase longevity, the first aim is not difficult to attain and in some elderly patients or those who lack motivation it is the only aim²⁵.

The major components of the treatment of diabetes are:

1. Insulin treatment
2. Diet (combined with exercise)
3. Oral hypoglycemic therapy

Insulin therapy: Insulin is a hormone produced by beta cells of the islets of Langerhans in the pancreas of animals, humans and synthetically. The proinsulin molecule undergoes a series of site-specific peptides cleavages that results in the formation of equimolar amounts of mature insulin and C peptide²⁶. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Considerable progress has been made in the production, formulation and delivery of insulin preparations, as well as the development of insulin treatment regimens which maintains long term normoglycemia, with a low risk of hypoglycemia²⁷.

Diet and exercise: The American Diabetes Association (ADA) promotes diabetes self-management education, a process in which the patient is equipped with the knowledge and skills to provide self-care, manage crisis (severe hyperglycemia and hypoglycemia), and make lifestyle changes. Diabetes self-management training is the process of educating the individuals that they enable to manage their diabetes which is considered an important part of clinical management²⁸. In fact, advice on diet and exercise are an important part of the treatment of type 2 DM. Overweight patients are advised to restrict calorie intake, consume food with low total fat content (especially saturated fat) and high (predominately unrefined) carbohydrate content. Type 2 diabetes individuals with moderate or high aerobic fitness have long-term mortality 50-60% lower than diabetic individuals with low cardiorespiratory fitness²⁹.

Current oral hypoglycaemic agents: The common strategy for treatment focused mainly on regulating and decreasing blood sugar to fall within the normal level. There are several types of glucose-lowering drugs, including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones) and α -glucosidase inhibitors (miglitol, acarbose)²⁷. Treatment of type 2 diabetes is based on interplay of patient characteristics, severity of hyperglycemia and available therapeutic options³⁰. Furthermore, hypoglycemic agents, such as incretin mimetics, dipeptidyl peptidase-4 inhibitors, and amylin analogues are also useful in adults and may soon be tested in children³¹.

Insulin secretagogues;

Sulfonylureas: These drugs produce their hypoglycemic actions via several mechanisms that can be broadly sub-classified as pancreatic and extra-pancreatic. Pancreatic Mechanism: All sulfonylurea hypoglycemics inhibit the efflux of K⁺ (K⁺ channel blockers) from pancreatic β -cells via a sulfonylurea receptor which may be closely linked to an ATP-sensitive K⁺ -channel. The inhibition of efflux of K⁺ leads to depolarization of the β - cell membrane and, as a consequence, voltage-dependent Ca⁺⁺-channels on the β -cell membrane then open to permit entry of Ca⁺⁺³². Cellular efflux of potassium is reduced and membrane depolarization takes place. Calcium influx is mediated by the opening of voltage-dependent Ca²⁺-channels that promote the release of pre-formed insulin granules which lie just adjacent to the plasma membrane³³. Sulfonylureas may also potentiate insulin action at target tissues (drug-dependent characteristic)³⁴.

Rapid- or short-acting secretagogues, also known as meglitinides, have a mode of action that is similar to that of the sulfonylureas. By closing the potassium channels of the pancreatic cells, they open the calcium channels and enhance insulin secretion. They were developed to have a rapid onset and short metabolic half-life, resulting in preferential targeting of post-prandial hyperglycemia and decreased risk for hypoglycemia later on³⁵.

Insulin sensitisers;

Biguanides (metformin): Metformin historic roots and origin can be traced back to the guanidine-rich *Galega officinalis* (goat's rue or French lilac) which has traditionally been used in Europe to treat diabetes. Metformin has a variety of clinical actions that extend beyond just the glucose lowering effects such as weight reduction, improving lipid profiles and vascular effects³⁶. However, it is thought that insulin sensitivity is improved and mediated via modification of postreceptor signaling in the insulin pathway. A

protein, adenosine 5'-monophosphate protein kinase, has been identified as a possible target of metformin³⁷. Moreover, Biguanides reduce hepatic glucose output and increase uptake of glucose by the peripheral tissues, including skeletal muscle.

Thiazolidinediones: Thiazolidinediones, such as pioglitazone and rosiglitazone, are agents that increase peripheral insulin sensitivity by increasing transcription of PPARs (peroxisome proliferator-activated receptors) that helps increase uptake of glucose, probably with effects on free fatty acid levels. Thiazolidinediones or TZDs act by binding to PPARs, a group of receptor molecules inside the cell nucleus, specifically PPAR γ (gamma)³⁸. The ligands for these receptors are free fatty acids (FFAs) and eicosanoids, when activated, the receptor migrates to the DNA, activating transcription of a number of specific genes. TZDs reverse insulin resistance by acting on muscle, fat and to a lesser extent liver to increase glucose utilization and diminish glucose production. Furthermore, TZDs, like metformin, require the presence of insulin to mediate a blood glucose-lowering effect³⁹.

The alpha-glucosidase inhibitors;

Acarbose: This class of drug has the advantage of reducing postprandial hyperglycemia without associated weight gain. They inhibit certain enzymes responsible for the breakdown of carbohydrates in the small intestine. They act mainly by decreasing the rate of carbohydrate absorption in the body⁴⁰. The α -glucosidase inhibitors inhibit the activity of the glucosidase enzymes which are present in the brush border of enterocytes in the intestinal villi. Disaccharide and oligosaccharide cleavage is prevented with a net decrease in intestinal carbohydrate absorption⁴¹. New peptide analogs, such as exenatide, liraglutide and dipeptidyl peptidase (DPP)-4 inhibitors, increase glucagon like peptide (GLP-1) serum concentration and slow down the gastric emptying⁴².

Adverse effects

Many of these oral antidiabetic agents have a number of serious adverse effects; thus, managing diabetes without any side effects is still a challenge⁴³. It includes risk of fracture and may also include fluid retention and peripheral edema as well as upper respiratory tract infection, sinusitis, and muscle or tooth pain. A high mortality rate has been shown when glyburide is used in combination with metformin⁴⁴. Meglitinide agents, Repaglinide and nateglinide may cause hypoglycemia as well as headache, nasal congestion, joint aches, back pain, constipation, and diarrhea⁴⁵. Most glucose-lowering drugs may have side effects, including severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache and dizziness⁴⁶.

Antidiabetic Herbal Agents

For thousands of year's natural products have played a very important role in health care and prevention of diseases. The ancient civilizations of the Chinese, Indians and North Africans provide written evidence for the use of natural sources for curing various diseases⁴⁷. In ancient Egypt, herbs are mentioned in Egyptian medical papyri, depicted in tomb illustrations, or on rare occasions found in medical jars containing trace amounts of herbs⁴⁸. In the early 19th century, when chemical analysis first became available, scientists began to extract and modify the active ingredients from plants.

These traditions are still flourishing; the World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Moreover, WHO estimates that about 4 billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care. Also, WHO notes that of 119 plant-derived pharmaceutical medicines, about 74 percent are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures⁴⁹. Indeed, about 25 percent of the prescription drugs dispensed in the United States contain at least one active ingredient derived from plant material. Some are made from plant extracts; others are synthesized to mimic a natural plant compound. Recently, it is encouraging to note that two drugs based on plant extract have been approved by the FDA for the treatment of human diseases. Veregen (Polyphenon E) Ointment is an extract of green tea as a prescription drug for the topical (external) treatment of genital warts caused by the human papilloma virus (HPV). Also, FDA's approved crofelemer (Fulyzaq) which derived from the latex of the South American sangre de drago tree as the first drug to be approved in the United States to treat HIV-associated diarrhea⁵⁰.

Traditional plant treatments have been used throughout the world for the therapy of diabetes mellitus. The ethanobotanical information reports about 800 plants that may possess antidiabetic potential and more than 1200 species of plants have been screened for activity on the basis of ethanopharmacology⁵¹. There is a continuous need to develop new and better pharmaceuticals as

alternatives for the management and treatment of the disease. Natural hypoglycemic compounds may be attractive alternatives to synthetic drugs or reinforcements to currently used treatments⁵². Therefore, in recent years, considerable attention has been directed towards identification of plants with antidiabetic ability that may be used for human consumption. Further, it emphasizes strongly in this regard the optional and rational uses of traditional and natural indigenous medicines⁵³.

Many herbal medicines have been recommended for the treatments of DM. Plants have been used traditionally throughout the world because of their effectiveness, less side effects and relatively low cost⁵⁴. There is urgent need therefore to fully explore these promising plants by carrying out further will further broaden the knowledge base on the various medicinal plants available for the management of diabetes mellitus.

Class of phytoconstituents

Several phytochemicals including alkaloids, flavonoids, glycosides, glycolipids, polysaccharides, peptidoglycans, carbohydrates, amino acids and saponins extracted from plant sources have been reported to possess hypoglycemic activity. Several phytochemicals may be found in a single plant and their combined synergistic action may be giving the observed behavior⁴⁶.

Alkaloids: Alkaloids are naturally occurring amines and they have pharmacological effects on humans and animals⁵⁵. Alkaloids are a structurally diverse group of over 12,000 cyclic nitrogen-containing compounds that are found in over 20% of plant species⁵⁶. Although no single classification exists, alkaloids are often distinguished on the basis of a structural similarity (e.g. indole alkaloids) or a common precursor (e.g. benzylisoquinoline, tropane, pyrrolizidine, or purine alkaloids)⁵⁷. This chemical group has contributed the majority of the poisons, neurotoxins, and traditional psychedelics (e.g. atropine, scopolamine, and hyoscyamine, from the plant *Atropa Belladonna*) and social drugs [e.g. nicotine, caffeine, methamphetamine (ephedrine), cocaine, and opiates] consumed by humans⁵⁸. Berberine (XI) is known to have potent hypoglycemic activity and it is found in *Tinospora cordifolia* (Willd.)⁵⁹.

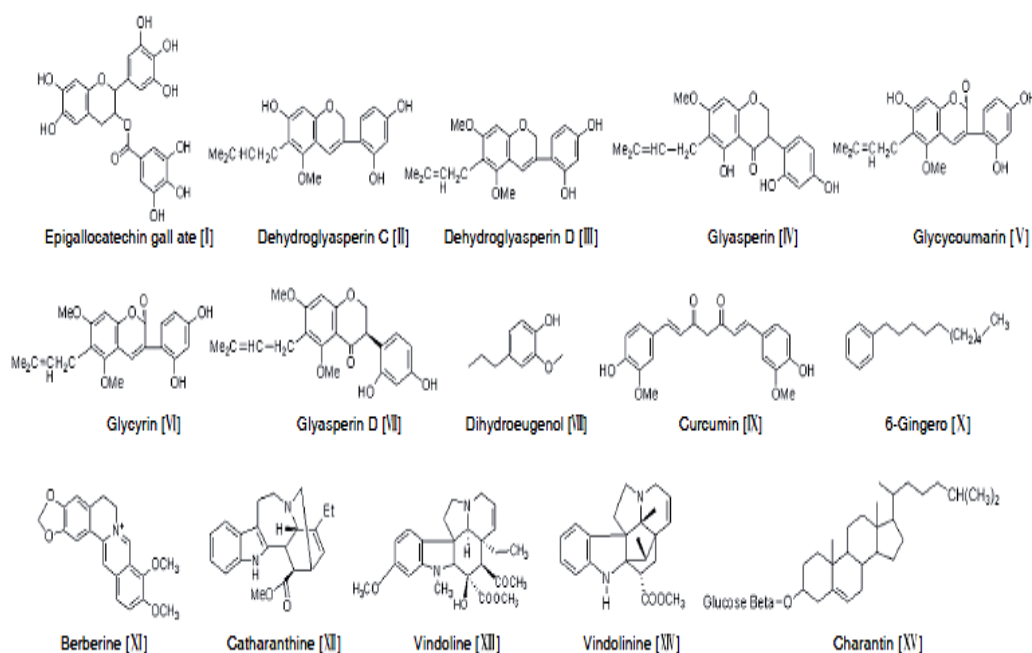


Figure 1: Phytochemicals with Hyperglycemic Activity⁶⁰.

Flavonoids: Flavonoids are a group of naturally occurring compounds which have hypoglycemic as well as antioxidant properties. They are also a class of plant secondary metabolites. Flavonoids can be widely classified into flavanols, flavones, catechins, flavanones, etc. They improve the glucose and oxidative metabolisms which is affected during diabetes. Quercetin is an important flavonoid known to increase hepatic glucokinase activity, probably by enhancing the insulin release from pancreatic islets⁶¹. It also exerts stimulatory effect on insulin secretion by changing Ca^{2+} concentration. Quercetin, Kaempferol and quercitrin are common flavonoids present in nearly 70% of plants. Genistein (XXIII) and soy isoflavonoids significantly improved the metabolism of lipid and glucose metabolism in obese Zucker rats by acting as a hypoglycemic on PPAR⁶². Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a flavonoid which is a highly abundant phenolic photochemical present in the cell walls of many plants that include *Curcuma longa* L. It may have significant health benefits through its antioxidant, anticancer and blood glucose lowering activities⁶³.

Polysaccharides: Polysaccharides are the most abundant and the most diverse materials found on earth. Drugs and health foods made of polysaccharides have been a research hotspot in the field of life sciences. The polysaccharide from *Salvia miltiorrhiza* Bunge can protect against the development of T2DM and improve insulin resistance via reduction of oxidative stress.

Polysaccharides feature prominently anti-diabetes in many Chinese herbs. Medicinal plants which include *Aloe vera* L., *Ocimum sanctum* L., and *Alpinagalanga* (L.) Willd contain polysaccharides which increase the insulin level and exhibit hypoglycemic properties. A protein bound polysaccharide isolated from pumpkin is shown to increase the levels of serum insulin, reduce blood glucose level and improve tolerance of glucose⁶⁴.

Saponins: Saponins are glycosides of steroids, steroid alkaloids (steroids with a nitrogen function) or triterpenoids found in plants. Charantin (XV), a steroidal saponin, isolated from *Momordica charantia* L. is reported to possess an insulin-like activity. Probably by enhancing the release of insulin and slowing down the glucogenesis. β -sitosterol (XVI), a steroid found in *Azadirachta indica* A. Juss; andrographolide (XVII), a diterpenoid lactone, isolated from *Andrographis paniculata* Nees⁶⁵ and saponingymnemic acid IV (XVIII), isolated from *Gymnema sylvestre* R, exhibit potent hypoglycemic activity in animal models⁶⁶.

Terpenes: Terpenes are a diverse group of more than 30,000 lipid-soluble compounds. Their structure includes 1 or more 5-carbon isoprene units, which are ubiquitously synthesized by all organisms through 2 potential pathways, the mevalonate and, more recently identified, deoxy-d-xylulose pathways⁶⁷. Terpenoids are classified according to the number of isoprene units they contain; isoprene, which itself is synthesized and released by plants, comprises 1 unit and is classified as a hemiterpene; monoterpenes incorporate 2 isoprene units, sesquiterpenes

incorporate 3 units, diterpenes comprise 4 units, sesterpenes include 5 units, triterpenes incorporate 6 units, and tetraterpenes 8 units⁶⁸. Terpenes can be used for the prevention and/or treatment of diabetes type II, obesity and neuropathy⁶⁹.

Phenolics: Phenolics are ubiquitously found across the plant kingdom, with ~10,000 structures identified to date. Structurally, they share at least 1 aromatic hydrocarbon ring with 1 or more hydroxyl groups attached. Of these, the flavonoids represent the largest, most diverse group, encompassing some 6000 compounds, all of which share a common underlying structure of two 6-carbon rings, with a 3-carbon bridge, which usually forms a 3rd ring. Flavonoids can then be subdivided according to modifications of this basic skeleton into chalcones, flavones, flavonols, flavanones, isoflavones, flavan-3-ols, and anthocyanins⁷⁰. It is used to treat albuminuria and diabetes⁶⁹.

Mechanism of Action of Medicinal Plants

Natural products are the major mine for discovering promising lead candidates, which play an important role in future drug development programs. Ease of availability, least side effects and low cost make the herbal preparations are the main key player of all available therapies, especially in rural areas⁷¹. Since centuries, many plants are considered a fundamental source of potent anti-diabetic drugs. Although, synthetic oral hypoglycemics together with insulin are the main route for controlling diabetes, however, they exhibited prominent side effects and failed to reverse the course of its complications. This constitutes the major force for finding alternatives, mainly from plant kingdom that are of less severe or even no side effects⁷².

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanisms of action of antidiabetic plants were summarized by¹ as the following;

1. Stimulation of insulin secretion from beta cells of islets.
2. Reduction in insulin resistance.
3. Stimulation of glycogenesis and hepatic glycolysis.
4. Inhibition in renal glucose reabsorption.
5. Providing certain necessary elements like calcium, zinc, magnesium, manganese, sulfur, selenium and copper for the beta-cells.
6. Protective effect on the destruction of the beta cells and help in increasing the size and number of cells
7. Regenerating and/or repairing pancreatic beta cells.

8. Prevention of pathological conversion of starch to glucose.
9. Inhibition of β -galactosidase and α -glucosidase
10. Inhibition of alpha-amylase.

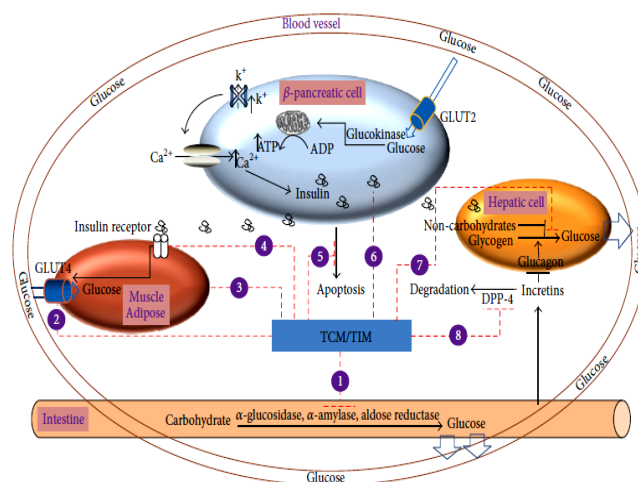


Figure 2: Mechanisms of antidiabetic effect of traditional Indian medicine and Chinese herbs. (1) Reduced carbohydrate absorption, α -glucosidase, α -amylase, and aldose reductase, (2) increased glucose uptake in muscle and adipose tissues, (3) activation of PPAR γ , (4) increased insulin sensitivity/upregulation of receptor expression, (5) exertion of antioxidant effects and decreasing β -cell apoptosis, (6) stimulation of β -cell insulin secretion, (7) inhibition of hepatic gluconeogenesis/glycogenolysis, and (8) prevention of endogenous incretins from degradation/suppression of glucagon⁵⁰.

Insulin secretion

Plants show hypoglycemic effect by increasing insulin secretion from beta cells of pancreas, *Allium cepa*, *Clerodendron phlomoides*, *Cinnamomum tamala*, *Coccinia indica*, *Encostemma littorale*, *Ficus bengalensis*, *Gymnema sylvestre* leaves, *Momordica charantia*, *Pterocarpus marsupium*, *Hibiscus rosa chinensis* and *Syzygium cumini*¹. Additionally, natural products classified into terpenoids, alkaloids, flavonoids, phenolics, and some other categories have shown antidiabetic potential through the insulinomimetic activity of the plant extract⁷³ (Table 2,3).

Allium cepa (Onion) and *Allium sativum* (Garlic)

They are important dietary supplements belonging to family *Liliaceae* that involved in the eastern kitchen. Studies showed that oral administration of the ethanol extract of garlic regulated the blood-sugar level, normalizing the activity of both liver hexokinase and glucose-6-phosphatase. In addition, it elevated liver glycogen, serum insulin as well as free amino acids, causing significant reduction in FBG, serum triglycerides, total

cholesterol⁷⁴. Many onion bulbs ether fractions showed significant hypoglycemic effects by decreasing the glucose peak in subcutaneous glucose tolerance tests⁷⁵. The hypoglycemic and hypolipidemic effects of onion were usually associated with a relevant antioxidant activity, as indicated by the increase in superoxide dismutase activity⁷⁶.

Hibiscus rosa chinensis

It is commonly called china rose belonging to family *malvaceae*. It stimulates insulin secretion from pancreatic beta cells and increases utilization of glucose either by direct stimulation of glucose uptake or the mediation of enhanced insulin secretion⁷⁷.

Eugenia jambolana

It is familiar by Jamun or black plum, belonging to family *Myrtaceae*. It is also known as *Syzygium cumini* and is widely being used over many centuries for the treatment of diabetes by the traditional practitioners. Oral administration of the pulp extract of the fruit resulted in the enhancement of insulinemia through insulin secretion stimulation and insulinase activity suppression from liver and kidney⁷⁵.

Insulin receptor;

Plants showed hypoglycemic effect by increases the expressions of insulin receptor in liver and skeletal muscle cells and improve cellular glucose consumption in the presence of insulin. Several plants give insulin sensitizers likes; Agaricus mushroom (*Agaricus blazei*) American ginseng (*Panax quinquefolius*) Banaba (*Lagerstroemia speciosa*) Cassia cinnamon (*Cinnamomum aromaticum*) Panax ginseng Prickly pear cactus (*Opuntia ficus-indica*) Soy (*Glycine max*), *Coptis chinensis*, *Tecoma stans* (*Bignoniaceae*) and *Teucrium cubense* (*Lamiaceae*)⁴⁶ (Table 2,3).

Coptis Chinensis

Coptis chinensis commonly used to treat diabetes in China. Berberine is an alkaloid and the active ingredient present in *Coptis chinensis*. It is found in plant roots, rhizomes, stems, and barks⁴⁶. Intra-gastric administration of berberine in diabetic rats decreased fasting blood glucose levels and total cholesterol, triglyceride and low density lipoprotein cholesterol and blocked the increment of superoxidase dismutase (SOD) and glutathione peroxidase (GSH-px) levels⁷⁸. It increases GLUT4 translocation in adipocytes and myotubes. It also increases the expressions of PPAR $\alpha/\delta/\gamma$ proteins in liver, ⁷⁹. Increases the expressions of insulin receptor in liver and skeletal muscle cells and improves cellular glucose consumption in the presence of insulin⁸⁰.

Tecoma stans (Bignoniaceae) and Teucrium cubense (Lamiaceae)

These plants were mainly used as a diabetes mellitus remedy. Their aqueous extracts exert a potent antidiabetic activity via enhancing glucose uptake in both insulin-sensitive and insulin-resistant murine and human adipocytes with no marked proadipogenic or antiadipogenic adverse effects⁸¹.

Cinnamomum zeylanicum

It is commonly known as Cinnamon (*Lauraceae*) and widely used in East Asia and Europe. It is extensively used in folk medicine to treat diabetes. It contains volatile oils, mainly cinnamaldehyde. Cinnamon ingestion decreased total plasma sugar level with insulin sensitivity improvement. It also significantly reduced gastric emptying and profoundly decreasing postprandial glycemic response⁸². In addition, cinnamon aqueous extract revealed a potent antidiabetic effect through its up regulation of uncoupling protein-1 (UCP-1) and enhancing the translocation of GLUT4 in the muscle and adipose tissues⁸³.

Trigonella foenum graecum

It is commonly known as “Fenugreek” in English and “Methi” in Hindi, is a member of family *Fabaceae*. *Trigonella foenum graecum* has antidiabetic activity in which the hypoglycemic effect has been confirmed by several investigators. In vitro effect of fenugreek extracts on intestinal sodium-dependent glucose uptake and hepatic glycogen phosphorylase⁸⁴.

Aegle marmelos

It is commonly called holy fruit tree belonging to family *Rutaceae*. It increases utilization of glucose either by direct glucose stimulation or by acting like insulin for glucose uptake⁸⁵. The antioxidant property of the *A. marmelos* leaf, play a vital role in delaying, intercepting or preventing oxidative reactions, catalyzed by free radicals. This antioxidant activity might be due to the presence of phenolic compounds such as flavonoids, phenolic acids and phenolic diterpenes⁸⁶.

Intestinal Blockers;

Plants show hypoglycemic effect by Reduction absorption of glucose from gastrointestinal tract, *Cyamopsis tetragonoloba*, *Ocimum sanctum* ⁸⁷. Bean pod (*Phaseolus vulgaris*), Blond psyllium (*Plantago ovata*), Fenugreek (*Trigonella foenum-graecum*), Glucomannan (*Amorphophallus konjac*), Guar gum (*Cyamopsis tetragonoloba*), Oat bran (*Avena sativa*), Prickly pear cactus (*Opuntia ficus-indica*), Soy (*Glycine max*), White mulberry (*Morus alba*) (Table 2, 3).

Mangifera indica

The tree is found throughout India and traditionally its seeds and fruits are used for treatment of various ailments. The extract showed antidiabetic

activity this action could be due to reduction in intestinal absorption of glucose⁸⁸. *Mangifera indica* has also been shown to exert powerful anti-oxidant activity in vitro⁸⁹.

Table 1: Classification of some herbal antidiabetics and current drugs according to their therapeutic action.

Therapeutic action	Drug name	Botanical name
Insulin secretion	Sulfonylureas (glibenclamide, gliclazide, glipizide, glimepiride)	<i>Eugenia jambolana</i> , <i>Pterocarpus marsupium</i> , <i>Medicago sativa</i> , <i>Biophytum sensitive</i> , Bitter melon (<i>Momordica charantia</i>), <i>Gymnema (Gymnema sylvestre)</i> , <i>Clerodendron phlomoides</i> , <i>Cinnamomum tamala</i> , <i>Coccinia indica</i> , <i>Encostemma littorale</i> , <i>Ficus bengalensis</i> , <i>Gymea sylvestre</i> leaves, <i>Momordica charantia</i> , <i>Eugenia jambolana</i> , <i>Syzygium cumini</i> , <i>Hibiscus rosa chinensis</i> .
	Biguanides (metformin) Thiazolidinediones (pioglitazone, rosiglitazone)	<i>Agaricus mushroom (Agaricus blazei)</i> , American ginseng (<i>Panax quinquefolius</i>), Banaba (<i>Lagerstroemia speciosa</i>), Cassia cinnamon (<i>Cinnamomum aromaticum</i>), Panax ginseng Prickly pear cactus (<i>Opuntia ficus-indica</i>), Soy (<i>Glycine max</i>), <i>Coptis chinensis</i> , <i>Tecoma stans</i> (<i>Bignoniaceae</i>), <i>Teucrium cubense (Lamiaceae)</i> <i>Cinnamomum zeylanicum (Lauraceae)</i> , Fenugreek (<i>Trigonella foenum-graecum</i>), <i>Aegle marmelos</i> .
Intestinal Blockers	Acarbose- Miglitol Glyset Voglibose	<i>Cyamposisteragonoloba</i> , <i>Ocimum sanctum</i> , Bean pod (<i>Phaseolus vulgaris</i>), Blond psyllium (<i>Plantago ovata</i>), Fenugreek (<i>Trigonella foenum-graecum</i>) <i>Glucomanan</i> , (<i>Amorphophallus konjac</i>), Guar gum (<i>Cyamopsis tetragonoloba</i>), Oat bran (<i>Avena sativa</i>) Prickly pear cactus (<i>Opuntia ficus-indica</i>) Soy (<i>Glycine max</i>), White mulberry (<i>Morus alba</i>).

Table 2: List of several hypoglycemic medicinal plants in Middle East.

	Botanical name	Common name	Family name	Activity	References
1.	<i>Aegle marmelos</i>	Bael fruits	<i>Rutaceae</i>	antidiabetic	77
2.	<i>Allium cepa</i>	Onion	<i>Liliaceae</i>	Hypoglycemic	75
3.	<i>Annona squamosa</i>	Sugar apple	<i>Annonaceae</i>	antidiabetic	90
4.	<i>Bambusa vulgaris</i>	Golden bamboo	<i>Graminae</i>	antidiabetic	91
5.	<i>Allium sativum</i>	Garlic	<i>Liliaceae</i>	Antihyperglycemic	92
6.	<i>Azadiracta indica</i>	Neem	<i>Meliaceae</i>	antidiabetic	93
7.	<i>Aloe vera</i>	Aloe	<i>Liliaceae</i>	antidiabetic	94
8.	<i>Coccinia indica</i>	Ivy	<i>Cucurbitaceae</i>	antidiabetic	95
9.	<i>Citrullus colocynthis</i>	Bitter apple	<i>Cucurbitaceae</i>	antidiabetic	96
10.	<i>Beta vulgaris</i>	Garden beet	<i>Chenipodiaceae</i>	antidiabetic	97
11.	<i>Ficus hispida</i>	Daduri	<i>Moraceae</i>	Antidiabetic	98
12.	<i>Canavalia ensiformis</i>	Horse bean	<i>Leguminosae</i>	Antidiabetic	99
13.	<i>Mucuna pruriens</i>	Velvet bean	<i>Leguminosae</i>	Antidiabetic	100
14.	<i>Hypoxis hemarocallidia</i>	-----	<i>Hypoxidaceae</i>	Antidiabetic	101
15.	<i>Punica granatum</i>	pomogranate	<i>Punicaceae</i>	Antidiabetic	102
16.	<i>Camellia sinensis</i>	Green tea	<i>Theaceae</i>	Antidiabetic	103
17.	<i>Trigonella foenum-</i>	Fenugreek	<i>Fabaceae</i>	antidiabetic	46
18.	<i>Acorus calamus</i>	Sweet Flag	<i>Acoraceae</i>	antidiabetic	104
19.	<i>Sclerocarya birrea</i>	Jelly plum	<i>Anacardiaceae</i>	antidiabetic	105
20.	<i>Embllica officinalis</i>	Indian Gooseberry	<i>Euphorbiaceae</i>	Hypoglycemic	106
21.	<i>Adansonia digitata</i>	baobab	<i>Malvaceae</i>	Hypoglycemic	107
22.	<i>Ficus glomerata</i>	Cluster fig tree	<i>Moraceae</i>	Hypoglycemic	108
23.	<i>Ficus religiosa</i>	Sacred tree	<i>Moraceae</i>	antidiabetic	109
24.	<i>Syzygium cumini</i>	Java plum	<i>Myrtaceae</i>	antidiabetic	110
25.	<i>Salvadora oleoides</i>	Salvadora	<i>Salvadoraceae</i>	antidiabetic	111
26.	<i>Solanum xanthocarpum</i>	yellow-fruit nightshade	<i>Solanaceae</i>	Antihyperglycemic	112
27.	<i>Vitex negundo</i>	five-leaved chaste tree	<i>Lamiaceae</i>	Antihyperglycemic	113
28.	<i>Alangium lamarckii</i>	-----	<i>Alangiaceae</i>	Antidiabetic	114
29.	<i>Axonopus compressus</i>	American carpet grass	<i>Poaceae</i>	Antidiabetic	115
30.	<i>Berberis vulgaris</i>	European barberry	<i>Berberidaceae</i>	Hypoglycaemic	116
31.	<i>Brassica juncea</i>	mustard greens	<i>Cruciferae</i>	Hypoglycaemic	117
32.	<i>Catharanthus roseus</i>	Madagascarperiwinkle	<i>Apocynaceae</i>	Hypoglycaemic	118
33.	<i>Centaurium erythraea</i>	common centaury	<i>Gentianaceae</i>	Antidiabetic	119
34.	<i>Chaenomeles sinensis</i>	Chinese Quince	<i>Rosaceae</i>	Antidiabetic	120
35.	<i>Costus speciosus</i>	Crebe ginger	<i>Costaceae</i>	Antidiabetic	121
36.	<i>Dillenia indica</i>	elephant apple	<i>Dilleniaceae</i>	Antidiabetic	46
37.	<i>Marrubium vulgare</i>	white horehound	<i>Lamiaceae</i>	Hypoglycaemic	122
38.	<i>Psidium guajava</i>	guava	<i>Myrtaceae</i>	Antihyperglycemic	123
39.	<i>Viscum schimperii</i>	-----	<i>Viscaceae</i>	Antihyper-glycemic	124
40.	<i>Encostemma littorale</i>	-----	<i>Gentianaceae</i>	Antidiabetic	125

41.	<i>Symplocos cochinchinensis</i>	-----	Symplocaceae	Antidiabetic	126
42.	<i>Vaccinium arctostaphylos</i>	Caucasian whortleberry	Ericaceae	antidiabetic	127
43.	<i>Acacia albida</i> Del.	Ana Tree	Mimosaceae	Antihyperglycemic	128
44.	<i>Citrus aurantium</i> L.	Bitter orange	Rutaceae	Antihyperglycemic	129
45.	<i>Citrus paradise</i> Macfad.	Grapefruit	Rutaceae	Antihyperglycemic	130
46.	<i>Mangifera indica</i> L.	Mango	Anacardiaceae	Antihyperglycemic	131
47.	<i>Mammea africana</i> Sabine.	African apple	Guttiferae	Antihyperglycemic	132
48.	<i>Ficus asperifolia</i> L.	Sand paper tree	Moraceae	Antihyperglycemic	133
49.	<i>Senna alata</i> L. Roxb.	Candle bush	Leguminosae	Antihyperglycemic	134
50.	<i>Vernonia colorata</i> Schreb.	Star-flowered bitter-tea	Compositae	Antihyperglycemic	6

Conclusion and Future of Medicinal Plants

Diabetes mellitus is a chronic disease which leads to various complications on long standing. The most serious problem is the side effect which occurs due to the accumulation of glucose which damages the vital organs and organelles. The global burden of diabetes is increasing worldwide as it is a costly disease for developing economies of the world. There are a number of plants which have the capacity to reduce the glucose production, induce the utilization of glucose and combat with secondary complications. Moreover, during the past few years some of the new bioactive drugs isolated from plants showed antidiabetic activity with more efficacy like oral hypoglycemic agents used in clinical therapy. The traditional medicine performed a good clinical practice and is showing a bright future in the therapy of diabetes mellitus.

Consequently, much effort should be afforded to optimize a procedure for antidiabetic screening of different plants extracts as well as isolated bioactive compounds for the discovery of new natural herbal antidiabetic drugs. For both the discovery of locally available alternative medicines to treat diabetics in developing countries, and for the commercial development of new botanical hypoglycemic agents and adjuncts to antidiabetic therapy, the best strategy will involve the study of traditional antidiabetic plants. During the development stage, product standardization, quality control and assurance, placebo-controlled and randomized clinical trials are essential components that need to be perfected in order to translate their potential into new antidiabetic drugs that millions of people could benefit upon.

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