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REVIEW ARTICLE

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-galactocidase and α–glucocidase 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; Antdiabetic 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 morbidity [3].

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 years [4]. The reasons for this global rise are growth of aged population, increasing trends towards obesity, unhealthy diet, and sedentary lifestyle[5]. 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 countries[6]. WHO estimated that diabetes resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death[7]. 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 productivity[8]. 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 administration[9].

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 mellitus[10].

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 blindness[11]. Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide[12].

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 individuals[10]. It eventually suppresses the synthesis of insulin receptor (a plasma membrane bound glycoprotein). Insulin resistance and insulin deficiency are common in the average NIDDM patients[13]. 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 NIDDM[14]. 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 diabetes[15].

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 delivery[16]. Insulin resistance and inadequate insulin secretion founded to play a central role in the pathophysiology of GDM[17]. Gestational diabetic women have increased risk of type 2 diabetes mellitus (T2DM) and heart disease later in life[18], and their offspring have greater incidence of perinatal complications and increased risk of obesity and diabetes in adulthood[19]. It usually disappears after the birth of child, and it affects 3-10% of pregnancies, depending on the population studied [20].

Diabetes due to other causes:

Genetic defect of β-cell function characterized by mutation in hepatocyte nuclear transcriptional factor (HNF) 4α, 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 cytomegalovirus[21].

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 blindness[22].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 dialysis[10]. 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 amputation[23].

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 cells[24]. 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 aim[25].

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 peptide[26]. 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 hypoglycemia [27].

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 management[28]. 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 fitness[29].

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 options[30]. 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 children[31].

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 ß-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 ß- cell membrane and, as a consequence, voltage-dependent Ca++-channels on the ß-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 membrane[33]. Sulfonylureas may also potentiate insulin action at target tissues (drug-dependent characteristic)[34].

Rapid- or short-acting secretagogs, 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 on[35].

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 effects[36]. 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 metformin[37]. 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 *PPARγ* (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 effect[39].

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 body[40]. 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 absorption[41]. 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 emptying[42].

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 challenge[43]. 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 metformin[44]. Meglitinide agents, Repaglinide and nateglinide may cause hypoglycemia as well as headache, nasal congestion, joint aches, back pain, constipation, and diarrhea[45]. Most glucose-lowering drugs may have side effects, including severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache and dizziness[46].

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 diseases[47]. 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 herbs[48]. 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 cultures[49].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 diarrhea[50].

Traditional plant treatments have been used throughout the world for the therapy of diabetes mellitus. The ethanobotonical 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 ethanopharmacology[51]. 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 treatments[52]. 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 medicines[53].

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 cost[54]. 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 behavior[46].

Alkaloids: Alkaloids are naturally occurring amines and they have pharmacological effects on humans and animals[55]. Alkaloids are a structurally diverse group of over 12,000 cyclic nitrogen-containing compounds that are found in over 20% of plant species[56]. 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 humans[58]. Berberine (XI) is known to have potent hypoglycemic activity and it is found in Tinospora cordifolia (Willd.)[59].

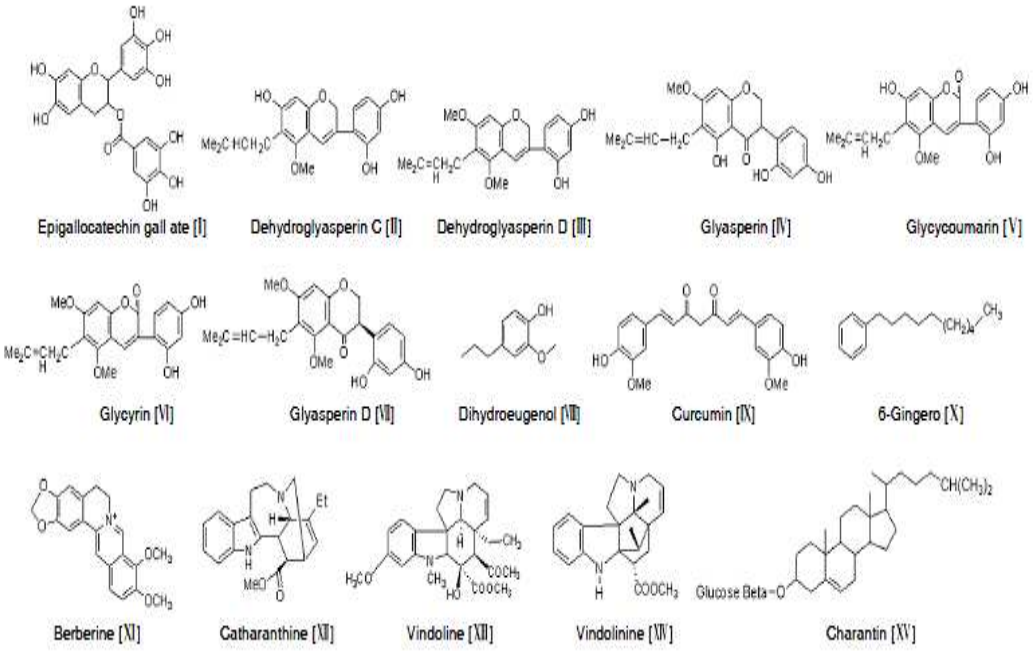

Figure 1: Phytochemicals with Hyperglycemic Activity[60].

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 islets[61]. It also exerts stimulatory effect on insulin secretion by changing Ca2+ 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 PPAR[62]. 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 activities[63].

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 *Alpiniagalanga (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 glucose[64].

Saponins: Saponins are glycosides of steroids, steroid alkaloids (steroids with a nitrogen function) or triterpinoids found in plants. Charantin (XV), a steroidal saponin, isolated from *Momordicacharantia 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 Azadirachtaindica A Juss; andrographolide (XVII), a diterpenoid lactone, isolated from Andrographispaniculata Nees[65] and saponingymnemic acid Ⅳ (XVIII), isolated from Gymnemasylvestre R, exhibit potent hypoglycemic activity in animal models[66].

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 pathways[67]. 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 units[68]. Terpenes can be used for the prevention and/or treatment of diabetes type II, obesity and neuropathy[69].

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 anthocyanins[70]. It is used to treat albuminuria and diabetes [69].

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 areas[71]. 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 effects[72].

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanisms of action of antidiabetic plants were summarized by[1] 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 -galactocidase and α–glucocidase
10. Inhibition of alpha-amylase.

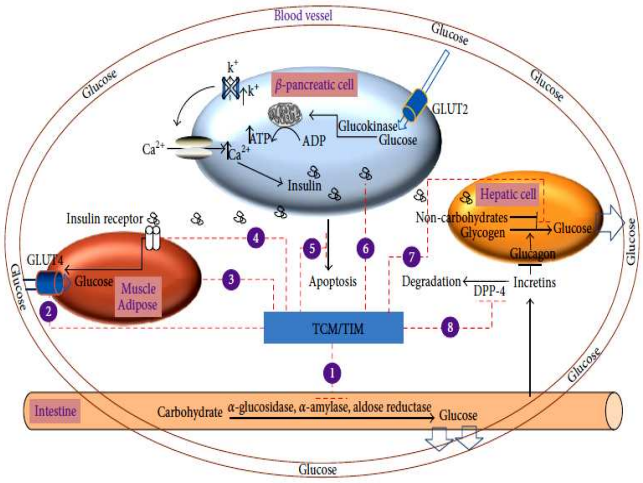

Figure 2: Mechanisms of antidiabetic effect of traditional Indian medicine and Chinese herbs. (1) Reduced carbohydrate absorption, α-glucosidase, α-amylase, and aldose reductase, (2) increased glucose uptake in muscle and adipose tissues, (3) activation of PPAR γ, (4) increased insulin sensitivity/upregulation 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 glucagon[50].

Insulin secretion

Plants show hypoglycemic effect by increasing insulin secretion from beta cells of pancreas, *Allium cepa*, *Clerodendron phlomoides*, *Cinnamomum tamala*, *Coccinia indica*, *Enicostemma 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 extract[73] (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

cholesterol[74]. Many onion bulbs ether fractions showed significant hypoglycemic effects by decreasing the glucose peak in subcutaneous glucose tolerance tests[75]. The hypoglycemic and hypolipidemic effects of onion were usually associated with a relevant antioxidant activity, as indicated by the increase in superoxide dismutase activity[76].

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 secretion[77].

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 kidney[75].

***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 chinensisis, Tecoma stans (*Bignoniaceae*) and Teucrium cubense (*Lamiaceae*)[46] (Table 2,3).

Coptis Chinensis

Coptis chinensisis commonly used to treat diabetes in China. Berberine is an alkaloid and the active ingredient present in *Coptis chinensisis*. It is found in plant roots, rhizomes, stems, and barks[46]. 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) levels[78]. It increases GLUT4 translocation in adipocytes and myotubes. It also increases the expressions of PPAR α/δ/γ 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 insulin[80].

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 effects[81].

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 response[82]. 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 tissues[83].

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 phosphorylase[84].

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 uptake[85].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 diterpenes[86].

Intestinal Blockers;

Plants show hypoglycemic effect by Reduction absorption of glucose from gastrointestinal tract, *Cyamposis tertragonoloba, 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 glucose[88]. *Mangifera indica* has also been shown to exert powerful anti-oxidant activity in vitro[89].

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)	*Eugeniajambolana Pterocarpus marsupium, Medicago sativa, Biophytum sensitive, Bitter melon (Momordica charantia), Gymnema (Gymnema sylvestre), Clerodendron phlomoides, Cinnamomum tamala, Coccinia indica, Enicostemma littorale, Ficus bengalensis, Gymea sylvestre leaves, Momordica charantia, Eugenia jambolana, Syzygium cumini, Hibiscus rosa chinensis.*
Insulin receptor Liver out put	Biguanides (metformin) Thiazolidinediones (pioglitazone, rosiglitazone)	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 chinensisis, Tecoma stans (*Bignoniaceae*), *Teucrium cubense* (*Lamiaceae*) *Cinnamomum zeylanicum* (*Lauraceae*), Fenugreek (*Trigonella foenum-graecum*), *Aegle marmelos.*
Intestinal Blockers	Acarbose- Miglitol Glyset Voglibose	*Cyamposistertragonoloba, Ocimum sanctum,* 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: List of several hypoglycemic medicinal plants in Middle East.

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

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

1. Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TP, Indian herbs and herbal drugs used for the treatment of diabetes, J Clin Biochem Nutr,2007,40,163-73.

2. World Health Organization (WHO), "About diabetes", Retrieved 4 April 2014.

3. Cade WT, Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting, Physical Therapy, 2008, 88(11), 1322-35.

4. Wild S., Roglic G, Green A, Sicree R, King H, Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes Care, 2004, 27(5), 1047-53.

5. Bagust A, Hopkinson PK, Maier W, Currie CJ, An economic model of the long-term health care burden of type 2 diabetes, Diabetologia,2001, 44, 2140-55.

6. Sy GY, Cissé A, Nongonierma RB, Sarr M, Mbodj NA, Faye B, Hypoglycaemic and antidiabetic activity of acetonic extract of *Vernonia colorata* leaves in normoglycaemic and alloxan-induced diabetic rats, J Ethnopharmacol, 2005,98(1–2),171–75

7. World Health Organization (WHO),"The top 10 causes of death, Fact sheet N°310, updated May 2014.

8. American Diabetes Association (ADA), The Cost of Diabetes, March 6, 2013 press release. http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.

9. Changxiao L, Constantinides PP, Yazhuo L, Research and development in drug innovation: reflections from the 2013 bioeconomy conference in China, lessons learned and future perspectives, Acta Pharmaceutica Sinica B ,2014, 4(2), 112–19.

10. Lakshmi M, Rani KS, Reddy T, A review on diabetes mellitus and the herbal plants used for its treatment, Asian Journal of Pharmaceutical and Clinical Research,2012, 5, 15-21.

11. Lindberg G, Lindblad U, Melander A, Sulfonylureas for treating type 2 diabetes mellitus. Cochrane Database Systemic Reviews volume 3, 2004.

12. American Diabetes Association (ADA), Diabetes report, 2001.

13. Holt G I, Diagnosis, epidemiology and pathogenesis of diabetes mellitus an update for Psychiatrists, Br J Psychiatry, 2004,184,s55- s63.

14. Raju SM, Raju B, Illustrated medical biochemistry, 2nd Edition, Jaypee Brothers Medical Publishers ltd, New Delhi, India, 2010, pp:645.

15. Wallace C, Reiber GE, LeMaster J, Smith DG, Sullivan K, et al., Incidence of falls, risk factors for falls, and fall-related factures in individuals with diabetes and a prior foot ulcer, Diabetes Care,2002,25,1983-86.

16. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, et al., Gestational diabetes and pregnancy outcomes-a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study

Groups (IADPSG) diagnostic criteria, BMC Pregnancy and Childbirth, 2012, 12(1), 23.

17. Buchanan TA, Xiang AH, Page KA, Gestational diabetes mellitus: risks and management during and after pregnancy, Nature Reviews Endocrinology, 2012, 8, 639-49.

18. Lee H, Jang HC, Park HK, Metzger BE, Cho NH, Prevalence of type 2 diabetes among women with a previous history of gestational diabetes mellitus, Diabetes research and clinical practice, 2008, 81, 124-29.

19. Metzger BE, Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring, Clinical obstetrics and gynecology, 2007, 50, 972-79.

20. Thomas RM, et al., Diabetes Mellitus and Pregnancy, med/2349 at eMedicine, Version, January 27, 2005.

21. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Diabetes mellitus, Harrison's Principles of internal medicines, 2005,16, 2152-80.

22. Svensson M, Eriksson JW, Dahlquist G, Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden, Diabetes Care, 2004,27, 955-62.

23. Amos A, McCarty D, Zimmet P, The rising global burden of diabetes and its complications, estimates and projections to the year 2010, Diabetic Med,2010,14, S1 S85.

24. Modi P, Diabetes beyond insulin: review of new drugs for treatment of diabetes mellitus, Curr Drug Discov Technol, 2007, 4,39-47.

25. Watkins PJ, Drury PL, Taylor KW, An Overview of management, In diabetes and its Management, ED Blackwell Scientific Publication, fourth edition,1990,pp, 63-66.

26. Mohammed, SA, Yaqub, AG, Sanda, KA, Nicholas, AO, Arastus, W, Muhammad, M and Abdullahi, S, Review on diabetes, synthetic drugs and glycemic effects of medicinal plants, Journal of Medicinal Plants Research,2013, 7(36),2628- 37.

27. Bolli GB, Hypoglycemia unawareness, Diabetes Metab, 1997, 23 (3), 29-35.

28. Stoffers DA, Ferrer J, Clarke WL, Habener JF, Early onset type-II diabetes mellitus (MODY) linked to IPF-1, Nature Genet, 1997, 17, 138-39.

29. Bastaki S, Review Diabetes mellitus and its treatment, Int J Diabetes & Metabolism, 2005, 13,111-34.

30. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, et al., Management of hyperglycaemia in type 2 diabetes, A patient-centered approach, position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia, 2012,55,1577–96.

31. Parkes DG, Pittner R, Jodka C, Smith P, Young A, Insulinotropic actions of exendin-4 and glucagons-like peptide-1 in vivo and in vitro, Metabolism ,2001,50,583-89.

32. Kawaki J, Nagashima K, Tanaka J, Miki T, Miyazaki M, Gonoi T, Mitsuhashi N, Nakajima N, IwanagaT, Yano H, Seino S, Unresponsiveness to glibenclamide during chronic treatment induced by reduction of ATP-sensitive K+ channel activity, Diabetes, 1990, 48 (10), 2001-06.

33. Aguilar-Bryan L, Nichols CG, Wechsler SW, Clement JP IV, Boyd AE III, Gonzalez G, Herrera-Sosa H, Nguy K, Bryan J and Nelson DA, Cloning of the beta cell high-affinity sulfonylurea receptor, A regulator of insulin secretion, Science, 1995,268,423–26.

34. Jack, D, Overview Of The Antidiabetic Agents, Endocrine Pharmacotherapy Module, 2003,1-33.

35. Nattrass M, Lauritzen T, Review of prandial glucose regulation with repaglinide: a solution to the problem of hypoglycaemia in the treatment of Type 2 diabetes?, Int J Obes Relat Metab Disord, 2000, 24(3),S21–31

36. Krentz AJ and Bailey CJ, Oral antidiabetic agents, current role in type 2 diabetes mellitus [review], Drugs, 2005, 65,385-411.

37. Shaw RJ, Lamia KA, Vasquez D, Koo SH, *et al.*, The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin, Science, 2005, 310(5754), 1642-46.

38. Kahn CR, Chen L, and Cohen SE, Unraveling the mechanism of action of thiazolidinediones, J Clin Invest, 2000, 106(11), 1305–07.

39. Demain AL and anchez S, Microbial drug discovery, 80 years of progress, J Antibiot (Tokyo), 2009, 62, 5-16.

40. DeFronzo RA, Pharmacologic therapy for type 2 diabetes mellitus, Ann Intern Med, 2000, 133(1), 73-74.

41. Chiasson JL, Acarbose for the prevention of diabetes, hypertension, and cardiovascular disease in subjects with impaired glucose tolerance: the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) Trial, Endocr Pract, 2006, 12 (1), 25-30

42. Gupta V, Glucagon-like peptide-1 analogues, An overview. Indian J Endocrinol Metab, 2013, 17(3), 413–21.

43. Saxena A, Vikram NK, Role of selected Indian plants in management of type 2 diabetes, a review, J Altern Complement Med,2004, 10(2),369–78

44. Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM, et al., Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin, Diabetes Metab Res Rev ,2006,22,477-482.

45. Repaglinide, MedMast Patient Drug Information Web site, Accessed July 9, 2008 Available at; http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=medmaster.chapter.a60001.

46. Kumar P, Doble M, Mechanism of Action of Natural Products Used in the Treatment of Diabetes Mellitus, Chin J Integr Med,2011, 17(8),563-574.

47. Phillipson JD, Phytochemistry and medicinal plants, Phytochemistry, 2001, pp, 237–43.

48. John N, Ancient Egyptian Medicine, University of Oklahoma Press, 2002, p, 151, ISBN 978-0-8061-3504-5.

49. Da-Silva EJ, Baydoun E, Badran A, "Biotechnology and the developing world", Electronic Journal of Biotechnology, 2002, 5 (1).

50. Wang Z, Wang J, Chan P, Treating Type 2 Diabetes Mellitus with Traditional Chinese and Indian Medicinal Herbs, Volume 2013, Article ID 343594, 17 pages

51. Patel DK, Kumar R, Lalu D, Natural medicines from plant source used for therapy of diabetes mellitus, An overview of its pharmacological aspects, Asian Pac J Trop Biomed,2012, 2 (3), 239-50.

52. Coman C, Rugina OD, Socaciu C, Plants and Natural compounds with Antidiabetic Action, Notulae Botanicae Horti Agrobotanici Cluj-Napoca, 2012, 40(1), 314-25.

53. Malviya N, Jain S, Malviya S, Antidiabetic Potential of Medicinal Plants, Acta Pol Pharm Drug Res ,2010,67(2),113-18.

54. Gurib-Fakim A, Medicinal plants, Traditions of yesterday and drugs of tomorrow Molecular Aspects of Medicine, 2006, 27 ,1–93.

55. Penumathsa SV, Thirunavukkarasu M, Zhan L, Maulik G, Menon VP, Bagchi D, et al. ,Resveratrol enhances GLUT-4 translocation to the caveolar lipid raft fractions ,through AMPK/AKT/eNOS signaling pathway in diabetic myocardium, J Cell Mol Med,2008,12,2350- 61.

56. Zulak K, Liscombe D, Ashihara H, Facchini P, Alkaloids, Plant secondary metabolism in diet and human health, Oxford, Blackwell Publishing,2006, p, 102–36.

57. Kennedy DO, Scholey AB, Wesnes KA, The dose-dependent cognitive effects of acute administration of Ginkgo biloba to healthy young volunteers. Psychopharmacology, 2000,151,416–23.

58. Zenk MH, Juenger M, Evolution and current status of the phytochemistry of nitrogenous compounds, Phytochemistry, 2007, 68, 2757–72.

59. Singh SS, Pandey SC, Srivastava S, Gupta VS, Patro B, Ghosh AC, Chemistry and medicinal properties of *Tinospora cordifolia* (Guduchi),Indian J Pharmacol ,2003,35,83-91.

60. Prabhakar PK, Doble M, Mechanism of Action of Natural Products Used in the Treatment of Diabetes Mellitus, Chin J Integr Med,2011,17(8),1-14.

61. Vessal M, Hemmati M, Vasei M, Antidiabetic effects of quercetin in streptozocin-induced diabetic rats, Comp Biochem Physiol C Toxicol Pharmacol,2003,135,357-64.

62. Mezei O, Banz WJ, Steger RW, Peluso MR, Winters TA, Shay N, Soy isofl avones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells, J Nutr ,2003,133,1238-43.

63. Ohnishi M, Matuo T, Tsuno T, Hosoda A, Nomura E,Taniguchi H, et al., Antioxidant activity and hypoglycemic effect of ferulic acid in STZ-induced diabetic mice and KK-Ay mice, Bio Factors,2004, 21,315-19.

64. Mukherjee PK, Maiti K, Mukherjee K, Houghton PJ, Leads from Indian medicinal plants with hypoglycemic potentials, J Ethnopharmacol,2006,106,1-28.

65. Yu BC, Hung CR, Chen WC, Cheng JT, Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats, PlantaMed 2003, 69, 1075-09.

66. Sugihara Y, Nojima H, Matsuda H, Murakami T, Yoshikawa M, Kimura I, Antihyperglycemic effects of gymnemic acid Ⅳ, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice, J Asian Nat Prod Res, 2000, 2,321-327.

67. Rohmer M, The discovery of a mevalonate-independent pathway for isoprenoid biosynthesis in bacteria, algae and higher plants, Nat Prod Rep, 1999,16,565–74.

68. De Martino L, Mancini E, de Almeida LFR, De Feo V, The antigerminative activity of twenty-seven monoterpenes, Molecules,2010 ,15:6630–7.

69. Makheswari UM, Sudarsanam D, Phytomedicine for Diabetes mellitus, An overview, Research in Pharmacy, 2011, 1(4), 28-37.

70. Bowsher CS, Tobin M, Plant Biochemistry A, New York, Garland Science, 2008.

71. Arya V, Gupta VK and Ranjeet K, A review on fruits having anti-diabetic potential, J Chem Pharmace Res, 2011, 3, 204-212.

72. Upendra Rao M, Sreenivasulu M, Chengaiah B, Jaganmohan Reddy K, Madhusudhana Chetty C, Herbal medicines for diabetes mellitus, a review, Int J Pharm Tech Res,2010, 2,1883-92.

73. Jung M, Park1 M, Chul L H, Kang Y, Kang E, Kim S, Antidiabetic Agents from Medicinal Plants, Current Medicinal Chemistry, 2006,13, 1203-18.

74. Goel R, Bhatia D, Gilani SJ , Katiyar D, Medicinal plants as antidiabetics, A review, Int Bull Drug Res, 2012,1, 100-7.

75. Grover JK, Vats V, Rathi SS, Dawar R,Traditional Indian antidiabetic plants attenuate renal hypertrophy, urine volume and albuminuria in streptozotocin induced diabetic mice,Journal of Ethnopharmacology,2001,76, 233–38.

76. Campos KE, Diniz YS, Cataneo AC, Faine LA, Alves MJQF, et al., Hypoglycaemic and antioxidant effects of onion, Allium cepa, dietary onionaddition, antioxidant activity and hypoglycaemic effects on diabetic rats, Int JFood sci Nut,2003, 54, 241-46.

77. Sachdewa A, Khemani D, A preliminary investigation of the possible hypoglycemic activity of Hibiscus rosa-sinensis, Biomedical and Environmental Sciences,1999, 12,222–26.

78. Hui H, Zhao X, Perfetti R, Structure and function studies of glucagon-like peptide-1 (GLP-1), The designing of a novel pharmacological agent for the treatment of diabetes1, Diabetes Metab Res Rev, 2005, 21,313-31.

79. Zhou L, Wang X, Shao L, Yang Y, Shang W, Yuan G, et al.,Berberine acutely inhibits insulin secretion from beta-cells through 3', 5'-cyclic adenosine 5'-monophosphate signaling pathway, Endocrinology,2008,149,4510-18.

80. Kong WJ, Zhang H, Song DQ, Xue R, Zhao W, Wei J,et al., Berberine reduces insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression, Metabolism ,2009,58(1),109-19.

81. Alonso-Castro AJ, Zapata-Bustos R, Romo-Yañez J, et al., The antidiabetic plants *Tecoma stans* (L.) *Juss. ex Kunth* (*Bignoniaceae*) and *Teucrium cubense Jacq* (*Lamiaceae*) induce the incorporation of glucose in insulin-sensitive and insulin-resistant murine and human adipocytes, J Ethnopharmacol, 2010,127, 1-6.

82. Subash-Babu P, Prabuseenivasan S, Ignacimuthu S, Cinnamaldehyde-A potential antidiabetic agent. Phytomed 14: 15-22.

83. Shen Y, Fukushims M, Ito Y, Muraki E, Hosono T, et al., Verification of the antidiabetic effects of cinnamon

(*Cinnamomum zeylanicum*) using insulin uncontrolled type 1 diabetic rats and cultured adipocytes, Biosci Biotechnol Biochem,2010, 74, 2418-25.

84. Al-Habori M, Raman A, Lawrence Mj, Pskett P, In Vitro Effect of Fenugreek Extracts on Intestinal Sodium-dependent Glucose Uptake and Hepatic Glycogen Phosphorylase A, Int. Jnl Experimental Diab,2001, Res, 2, 91-99.

85. Das AV, Padayatti PS, Paulose CS, Effect of leaf extract of *Aegle marmelose (L.) Correa ex Roxb* on histological and ultrastructural changes in tissues of streptozotocin induced diabetic rats, Ind J Exp Biol, 1996, 34, 341-45.

86. Sur T, Pandit S, Pramanik T, Antispermatogenic activity of leaves of *Aegle marmelos*, *corr*, In albino rats, a preliminary report, Biomed, 1999, 19,199-202.

87. Tripathi Ak, Bhoyar PK, Baheti JR, Biyani DM, Khalique M, et al., Herbal antidiabetics, A review, Int J Res Pharm Sci,2011, 2,30-37.

88. Aderibigbe, AO, Emudianughe, TS, Lawal, BA, Antihyperglycaemic effect of *Mangifera indica* in rat, Phytother Res, 1999, 13(6),504-7.

89. Martinez, G, Delgado, R, Perez, G, Garrido, G, Nunez Selles, AJ, Leon, OS, Evaluation of the in vitro antioxidant activity of *Mangifera indica L* extract, Phytotherapy Research ,2000,14 (6), 424-27.

90. Gupta RK, Kesari AN, Murthy PS, Chandra R, Tandon V, Watal G, Hypoglycemic and antidiabetic effect of ethanolic extract of leaves of *Annona squamosa* L in experimental animals, J Ethnopharmacol, 2005,99,75-81.

91. Fernando MR, Tabrew MI, Karunanayake EH, Hypoglycaemic activity of some medicinal plants in Sri-Lanka, Gen Pharmacol ,1999,21, 779-82.

92. Jain RC and Vyas, CR, Garlic in alloxan-induced diabetic rabbits, American Journal of Clinical Nutrition, 1975, 28, 684–85.

93. Chattopadhyay RR, A comparative evaluation of some blood sugar lowering agents of plant origin, J Ethnopharmacol, 1999, 67,367-72.

94. Rajasekaran, S, Sivagnanam, K, Ravi, K, Subramanian, S, Hypoglycemic effect of *Aloe vera gel* on streptozotocin-induced diabetes in experimental rats, Journal of Medicinal Food,2004, 7, 61–66.

95. Platel, K, Srinivasan, K, Plant foods in the management of diabetes mellitus, vegetables as potential hypoglycemic agents, Die Nahrung,1997,41,68–74.

96. Al-Ghaithi, F, El-Ridi, MR, Adeghate, E and Amiri, MH, Biochemical effects of *Citrullus colocynthis* in normal and diabetic rats, Molecular and Cellular Biochemistry,1995, 261,143–49.

97. Yoshikawa, M, Murakami, T, Kadoya, M, Matsuda, H, Muraoka, O, Yamahara, J, Murakami, N, Medicinal foodstuff III Sugar beet, Hypoglycemic oleanolic acid oligoglycosides, betavulgarosides I, II, III, and IV, from the root of *Beta vulgaris L (Chenopodiaceae),* Chemical and pharmaceutical Bulletin (Tokyo),1996, 44, 1212–17.

98. Ghosh R, Sharachandra KH, Rita S, Thokchom IS, Hypoglycemic activity of *Ficus hispida* (bark) in normal and diabetic albino rats, Indian J Pharmacol,2004, 36, 222 .

99. Enyikwola O, Addy EO, Adoga GI, et al., Discov. Innovat, 1991, 3, 61.

100. Grover JK, Vats V, Rathi SS, Dawar R, Traditional Indian antidiabetic plants attenuate renal hypertrophy, urine volume and albuminuria in streptozotocin induced diabetic mice, Journal of Ethnopharmacology, 2001, 76, 233–238.

101. Bahle S, John A O, Med J I, AcadSci, 2000, 13, 75 .

102. Jafri, MA, Aslam, M, Javed, K, Singh, S, Effect of *Punica granatum Linn* (flowers) on blood glucose level in normal and alloxan-induced diabetic rats, Journal of Ethnopharmacology, 2000,70, 309–14

103. Anderson RA and Polansky MM, Tea enhances insulin activity, Journal of Agricultural and Food Chemistry, 2002,50, 7182–86.

104. Prisilla D H, Balamurugan R, Shah H R, Antidiabetic activity of methanol extract of *Acorus calamus* in STZ induced diabetic rats, Asian Pac J Trop. Med, 2012, 2- S941.

105. Dimo T, Rakotonirina S V, Tan P V, Azay J, Dongo E, Kamtchouing P, Cros G, Effect of *Sclerocarya birrea* stem bark methylene chloride/methanol extract of streptozotocin-induced diabetic rats, J Ethnopharmocol, 2007,110, 434.

106. Madar Z, Rachel A, Shlomith S, Joseph A, Glucose lowering effect of fenugreek in noninsulin dependent diabetics, Eur J Clin. Nutr, 1988,42,51.

107. Tanko Y, Okasha M A, Magaji G M, Yerima M, Yaro A H, Saleh M I A & Mohamme A, Anti – diabetic properties of *Securinega virosa (Euphorbiaceae)* leaf extract, Afr J Biotechnol, 2008,7,022.

108. Sharma V K, Kumar S, Patel H J, Hugar S, Hypoglycaemic activity of *Ficus glomerata* in Alloxan induced diabetic rats, Int J Pharm Sci Res, 2010, 118.

109. Pandit R, Phadke A, Jagtap A, Antidiabetic effect of *Ficus religiosa* extract in streptozotocin-induced diabetic rats, J Ethnopharmacol, 2010, 128, 462-66.

110. Kumar A, Ilavarasan R, Jayachandran T, Deecaraman M, Aravindhan P, Padmanabhan N, Krishan MRV, Anti-diabetic activity of *Syzygium cumini* and its isolated compound against streptozotocin-induced diabetic rats, Journal of Medicinal Plants Research, 2008, 2, 246-49.

111. Yadav JP, Saini S, Kalia AN, Dangi AS, Hypoglycemic and hypolipidemic activity of ethanolic extract of *Salvadora oleoides* in normal and alloxan-induced diabetic rats, Indian Journal of Pharmacology 2008,40(1),23-27.

112. Poongothai K, Ponmurugan P, Ahmed K S Z, Kumar S B, Sheriff S A, Antihyperglycemic and antioxidant effects of *Solanum xanthocarpum leaves* (field grown & in vitro raised) extracts on alloxan induced diabetic rats, Asian Pac J Trop,2011, 778.

113. Sundaram R, Naresh R, Shanthi P, Sachdanandam P, Antihyperglycemic effect of iridoid glucoside, isolated from the leaves of *Vitex negundo* in streptozotocininduced diabetic rats with special reference to glycoprotein components, Phytomedicine,2012, 19(3-4), 211-16.

114. Kumar R, Patel DK, Prasad SK, Laloo D, Krishnamurthy S, Hemalatha S, Type 2 antidiabetic activity of bergenin from the roots of *Caesalpinia digyna Rottler*, Fitoterpia,2012, 83, 395-401.

115. Ibeh BO, Ezeaja MI, Preliminary study of antidiabetic activity of the methanolic leaf extract of Axonopus compressus (P. Beauv)

in alloxan-induced diabetic rats, J Ethnopharmacol, 2011, 8,138(3),713-16.

116. Meliani N, Amine Dib ME, Allali H, Tabti B, Hypoglycaemic effect of *Berberis vulgaris* L in normal and streptozotocin induced diabetic rats, Asian Pac J Trop Biomed, 2011, 6,468-71.

117. Thirumalai T, Therasa VS, Elumalai EK, David E, Hypoglycemic effect of *Brassica juncea* (seeds) on streptozotocin induced diabetic male albino rat, Asian Pac J Trop Biomed, 2011, 4, 323-25.

118. Ohadoma SC, Michael HU, Effects of co-administration of methanol leaf extract of *Catharanthus roseus* on the hypoglycemic activity of metformin and glibenclamide in rats, Asian Pac J Trop Med, 2011, 475-77.

119. Sefi M, Fetoui H, Lachkar N, Tahraoui A, Lyoussi B, Boudawara T, et al., *Centaurium erythrea (Gentianaceae)* leaf extract alleviates streptozotocin-induced oxidative stress and b-cell damage in rat pancreas, J Ethnopharmacol., 2011, 135,243-50.

120. Sancheti S, Sancheti S, Seo SY, Antidiabetic and antiacetylcholin esterase effects of ethyl acetate fraction of *Chaenomeles sinensis (Thouin)* Koehne fruits in streptozotocin-induced diabetic rats, Exp Toxicol Pathol, 2011, 65(1-2), 55-60.

121. Eliza J, Diasy P, Ignacimuthu S, Duraipandiyan V, Antidiabetic and antilipidemic effect of eremanthin from *Costus speciosus* (Koen.)Sm, in STZ-induced diabetic rats, Chem Biol Interact, 2009,182, 67-72.

122. Elberry AA, Harraz FM, Ghareib SA, Gabr SA, Nagy AA, Sattar EA, Methanolic extract of *Marrubium vulgare* ameliorates hyperglycemia and dyslipidemia in streptozotocin-induced diabetic rats, Int J Diabetes Mellitus, Available online 5 February 2011.

123. Huang CS, Yin MC, Chiu LC, Antihyperglycemic and antioxidative potential of *Psidium guajava* fruit in streptozotocin-induced diabetic rats,Food Chem Toxicol ,2011,41, 2189-95.

124. Sattar EA, Elberry AA, Harraz FM, Ghareib SA, Nagy AA, Gabr SA, Antihyperglycemic and hypolipidaemic effects of the methanolic extract of Saudi mistletoe (*Viscum schimperi Engl*),J Adv Res,2011, 2, 171-77.

125. Sonawane RD, Vishwakarma SL, Lakshmi S, Rajani M, Padh H, Goyal RK ,Amelioration of STZ-induced type 1 diabetic nephropathy by aqueous extract of *Enicostemma littorale Blume* and swertiamarin in rats, Mol Cell Biochem ,2010, 340, 1-6.

126. Sunil C, Ignacimuthu S, Agastian P, Antidiabetic effect of *Symplocos cochinchinensis* (Lour) S Moore, in type 2 diabetic rats, J Ethnopharmacol,2011, 134, 298–304.

127. Feshani, AM, Koushari SM, Mohammadi S,Vaccinium arctostaphylos, a common herbal medicine in Iran, Ethnofarmacology, 2011,133,67- 74.

128. Salisu Y, Agunu A, Abubakar MS, Ibrahim G, Hypoglycaemic effects of *Acacia albida Del* (*Mimosaceae*) methanol root bark extract, Niger J Pharm Sci, 2009, 8, 66–72.

129. Opajobi AO, Esume CO, Campbell P, Onyesom I, Osasuyi A, Effects of aqueous extracts of *Rauvolfia vomitoria* and *Citrus aurantium* on liver enzymes of streptozotocin – induced diabetic and normal rabbits, Cont J Med Res 2011, 5, 1–5.

130. Adeneye AA,Hypoglycemic and hypolipidemic effects of methanol seed extract of *Citrus paradisi Macfad (Rutaceae*) in alloxan-induced diabetic Wistar rats, Niger Q J Hosp Med ,2008, 18, 211–215

131. Ugbenyen AM, Odetola AA, Hypoglycemic potential of the young leaves methanolic extract of *Magnifera indica* in alloxan induced diabetic rats, Pak J Nutr 2009, 8, 239–41.

132. Okokon JE, Bassey SA, Osuji LC, Pius MU, Antidiabetic and hypolipidemic effect of *Mammea africana* (*Guttiferae*) in streptozotocin induced diabetic rats, J Pharmacol Toxicol ,2007, 2, 278–83.

133. Omoniwa BP, Luka CD, Antidiabetic and toxicity evaluation of aqueous stem extract of *Ficus asperifolia* in normal and alloxan-induced diabetic rats, Asian J Exp Biol Sci, 2012, 3, 726–32.

134. Kolawole OM, Oladoyinbo SO, Agbede OO, Adu FD, The effect of *Bridelia ferruginea* and *Senna alata* on plasma glucose concentration in normoglycemic and glucose induced hyperglycemic rats, Ethnobot Leaflets, 2006, 10, 209–18.

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