# Mode of action of medicinal plants on diabetic disorders

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**Abstract:** Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyperlipedemia, hyperaminoacidemia, and hypoinsulinaemia it leads to decrease in both insulin secretion and insulin action, along with varying degrees of peripheral resistance to the action of insulin. The long-term effects of impaired glucose regulation can lead to permanent organ damage, such as cardiovascular disease, and disabilities. Nowadays, there is growing interest in medicinal herbs due to the side effects associated with the therapeutic agent for the treatment of diabetes mellitus. In addition therapeutic action of herbal medicines is due to the herbal ingredients mechanism, bioactive compounds of most of the plants have been isolated and identified. However, mechanisms of action of most plants and their products that used for lowering of blood glucose remain unknown. in this study by searching in different sources and references such as Pub Med, MEDLINE, CNKI, EMBASE, Wiley Inter Science, Elsevier data bases, tried to express mode of action some common medicinal herbs that have important role in lowering of blood glucose and diabetics recovery.
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**Key words:** Diabetic, Medicinal plant, Mechanism, Bioactive, Metabolism, Insulin.

## Introduction:

Diabetes mellitus is a metabolic disorder characterized by failure of glucose homeostasis with disturbances of carbohydrate, fat and protein metabolism resulting defects in insulin secretion, insulin action, or both. Without enough insulin, body tissues, particularly, the liver, muscle and adipose tissues fail to take and utilize glucose from the blood circulation. This results in elevated blood glucose levels, a condition known as hyperglycemia. If blood glucose levels remain high over a long period of time, this can result in long-term damage of organs such as the kidneys, eyes, nerves, heart and blood vessels. Complications in some of these organs can lead to death [1-3].

Currently, type 2 diabetes mellitus, the most common type of diabetes mellitus, is managed by a combination of diet, exercise, oral hypoglycemic drugs and sometimes insulin injections [4]. However, synthetic oral hypoglycemic drugs, which are currently the main form of treatment for type 2 diabetes mellitus have been shown to have undesirable side effects and high secondary failure rates [4]. In addition, these drugs cannot be afforded by the majority of people living in rural communities of developing countries because of their high cost [4]. These limitations, of currently available antidiabetic pharmacological agents have prompted researchers all over the world to investigate alternative antidiabetic remedies. In particular, consideration is given to plants and herbs used by traditional healers and herbalists as antidiabetic remedies with the hope of discovering new natural products that can be used or developed into safe, inexpensive and effective antidiabetic remedies. For their hypoglycemic potential using experimental animal models of diabetes [5-7] as well clinical studies involving diabetic patients [8-10]. In addition, bioactive compounds of most of these plants have been isolated and identified [10, 11]. However, mechanisms of action whereby most of these plants and their products exert their blood glucose lowering effects on tissue or organs remain unknown.

## Methods:

We searched for papers published in Pub Med, MEDLINE, CNKI, EMBASE, Wiley Inter Science, Elsevier data bases. In this context, a number of medicinal plants and herbs have been studied and validated assess without language limit by retrieving key words “Diabetic, Medicinal plant, Mechanism, Bioactive, Ingredient, Insulin, phytochemistry, complication, carbohydrate, metabolism,” to identify mechanism and mode of action of medicinal plants on diabetics disorders. These searches were conducted by two independent examiners. The last date of the search was January 28, 2012.

## Results:

**Type 2 diabetes mellitus**; commonly known as non-insulin diabetes mellitus occurs in adult patients aged 40 years and above, is a polygenic disorder with

obesity related insulin resistance playing a major role in its onset and progression. It is characterized by excessive hepatic glucose production, decreased insulin secretion from pancreatic beta cells, and insulin resistance in peripheral tissue such as muscle adipose and liver [12]. There are convincing data to indicate a genetic component associated with insulin resistance. Insulin resistance is a feature of the offspring of parents with type 2 diabetes. In Pima Indians, a group with a very high prevalence of insulin resistance and type 2 diabetes, the insulin resistance has been suggested to have a co-dominant mode of inheritance [13]. Insulin resistance is also caused by acquired factors such as obesity, sedentary life style, pregnancy, and hormone excess. During its early stage, insulin resistance is compensated for by hyperinsulinemia, thus preserving normal glucose tolerance. Deterioration into impaired glucose tolerance occurs where either insulin resistance increases or the insulin secretory responses decrease, or both [14].

**Popularity of diabetes mellitus**

Currently, the overall global prevalence of diabetes is estimated to be between 3.0% and 3.6% of the population, of which 90% is type 2 diabetes [15, 16] In this context, the prevalence of diabetes for all age groups worldwide was estimated to be 2.0% in 1997[15], 2.8% in 2000 [16] and 3.6% in 2010 [15] and was projected to be 4.4% (366 million people) in 2030 [16]. The prevalence of diabetes is reported to be higher in men than in women; however, there are more women than men with diabetes [16]. Population growth, urbanization, increasing prevalence of obesity and physical inactivity are thought to be the main factors responsible for the increasing prevalence of type 2 diabetes mellitus [16-18].

**Complications of diabetes mellitus**

Uncontrolled hyperglycemia in type2 diabetes leads to the development of both acute and long term complications [3]. Acute complications of diabetes mellitus include non ketotic hyperosmolar coma. Long term complications include cardiovascular diseases, hypertension, chronic renal failure, retinal damage, nerve damage, erectile dysfunction and macrovascular damage which may cause poor healing of wounds particularly of the feet and can lead to gangrene which may require amputation. Chronically elevated blood glucose levels lead to increase production of mitochondrial reactive oxygen species (ROS), which activate a number of metabolic pathways whose end products contribute to the development of long term complication of diabetes [3, 19]. These metabolic pathways activated by hyperglycemia-induced ROS include: the polyol pathway, formation of advanced glycation end product (AGE), hexosamine pathway and the protein kinase C (PKC) pathway [20-25].

**Treatment of type 2 diabetes mellitus**

The chronic hyperglycemia of diabetes can lead to health complications such as blindness, gangrene, kidney failure, heart attacks and strokes, which are devastating to the individual and very expensive to the health services [1, 26, 27] Available evidence indicates that diabetes related complications can be prevented or delayed by achieving tight glycemic control [28].Therefore, much effort has been devoted to the search and development of optimal therapeutic regimens for the management of diabetes. Currently, type 2 diabetes is controlled and managed by a combination of diet restriction, weight reduction programs and oral hypoglycemic drugs [4]; Orally administered hypo-glycemic agents (e.g. sulfonylureas, repaglinide, metformin, alpha glucosidase inhibitors and thiazolidinediones (TZDs) are used first together with dietary restriction and exercise programs [4]. When hyperglycemia becomes severe, patients are usually switched to insulin injections, with or without oral agents to improve insulin action [4] However, current anti-diabetic medications have toxic side effects including, but not limited to, nausea, diarrhea, and hypoglycemia at higher doses, liver problems, lactic acidosis and weight gain. These side effects prompt patients to stop taking these anti-diabetic medications. Furthermore, despite the intensive use of current anti-diabetic agents, many type 2 diabetic patients still exhibit poor glycemic control and some develop serious complications within six years of diagnosis [26]. Clearly, there is a need for new anti-diabetic agents.

**Mode of action of hypoglycemic medicines**

Oral hypoglycemia agents exert their glucose lowering effects via a variety of mechanisms. These mechanisms of action include reduction of hepatic glucose production, (metformin, a biguanide), enhancement of insulin secretion by pancreatic beta cells, improvement of insulin sensitivity and inhibition of intestinal glucose digestion and absorption (alpha glucosidase inhibitors). The use of these drugs is however, limited by the fact that they have adverse side effects, such as potential hypoglycemia (e.g. sulfonylurea), weight gain (meglitinides, sulfonylurea and thiazolidinesdiones), gastro-intestinal discomforts (alpha glucosidase inhibitors, and alpha amylase inhibitors) and lactoacidosis (metformin) [29] In addition to their potential side effects, many of the oral anti-diabetic agents have higher secondary failure rates [4].

**Medicinal plants for diabetes**

As is the case with other diseases, medicinal plants have been used since ancient times to treat and manage diabetes mellitus in traditional medical systems of many cultures throughout the world [30, 31]Currently, medicinal plants continue to play an important role in the management of diabetes mellitus, especially in developing countries, where many people do not have access to conventional antidiabetic therapies [11] [32]. In developed countries the use of antidiabetic herbal remedies is reported to have been declining since the introduction of insulin and synthetic oral hypoglycemic agents during the early part of the twentieth century. However, in recent years, there has been a resurgence of interest in medicinal plants with hypoglycemic potential in these countries. This renewed interest in herbal antidiabetic remedies in developed countries is believed to be motivated by several factors, including, the side effects, high secondary failure rates and the cost of conventional synthetic antidiabetic remedies [31]. Ethnopharmacological surveys indicate that more than 1200 plants are used in traditional medical systems for their alleged hypoglycemic activity [33].The hypoglycemic activity of a large number of these plants products has been evaluated and confirmed in animal models [6, 34] as well as in human beings [8-10] In some cases the bioactive principles have also been isolated and identified [5, 10, 11]. However, the mechanism of action of the most products, lower the blood glucose level, remain speculative.

**Most studied antidiabetic medicinal plants**

The most studied and commonly used medicinal plants whose blood glucose lowering effects have been tested and confirmed in different parts of the world include: Allium cepa (Onion), Allium sativum (Garlic), Aloe vera, Cinnamomum tamala, Coccinia indica, Gymnema sylvestre (Gurmar), Momordica charantia (Bitter Melon), Murrayi koningii, Ocimum sanctum, Panax (Asian) Ginseng, Trigonella foenum-graecum (Fenugreek), Pterocarpus marsupium (Indian Kino) and Syzigium cumini [35-43].

**Bioactive constituents of antidiabetic medicinal plants**

Ivorra et al [44] cited by Tanira, [45], studied the structure of 78 different compounds isolated from plants with attributed hypoglycaemic activity. They classified these compounds according to the following chemical groups: 1. Polysaccharides and proteins (59 com-pounds), 2. Steroids and terpenoids (7compounds), 3. Alkaloids (7compounds), 4. Flavonoids and related compounds (5 compounds). Similarly, Bailey and colleague [30] listed 29 compounds that contained 14 polysaccharides, 5 alkaloids 4 glycosides and 6 other compounds. Grover and colleague [11] reviewed 45 medicinal plants of India with confirmed antidiabetic potential. Of the 17 hypoglycemic principles isolated and identified in this review 5 compounds are amino acids and related compounds, 5 compounds are glycosides, and 3 compounds are phenolic (flavonoids) compounds. The remaining compounds are alkaloids (2 compounds), terpenoids (1 compoud) and polysaccharides (1compound). Bnouham [46, 47] also reviewed 178 with potential antidiabetic activity. The 56 hypoglycemic principles identified in this review belong to the following chemical groups: 1. Glycosides (mostly saponins) (24 compounds). 2. Phenolics (mostly flavonoids) (11 compounds) 3.Polysaccharides (9 compounds) 4.Terpernoids (5 compounds) 5.Amino acids and related compounds (4 compounds) 6.Alkaloids (3 compounds).

It can be concluded on the basis of these four studies that a variety of phytochemicals possess hypoglycemic activity. However, the majority of plants with blood glucose lowering activity appear to contain polysaccharides, glycosides and flavonoids. Another point of note in the above mentioned review studies is that a given plant and its product may possess more than one hypoglycemic principles which may act in synergy to exert a blood glucose lowering effect.

**Mechanism of action of antidiabetic medicinal plants and their constituents**

There are several possible mechanisms through which these herbs can act to control the blood glucose level [45]. The mechanisms of action can be related, generally, to the ability of the plant in question (or its active principle) to lower plasma glucose level by interfering with one or more of the processes involved in glucose homeostasis. The reported mechanisms whereby herbal antidiabetic remedies reduce blood glucose levels are more or less similar to those of the synthetic oral hypoglycemic drugs and are summarized as follows [45-48]: 1. Stimulation of insulin synthesis and secretion from pancreatic beta-cells. 2. Regeneration/revitalization of damaged pancreatic beta cells. 3. Improvement of insulin sensitivity (enhancement of glucose uptake by fat and muscle cells). 4. Mimicking the action of insulin (acting like insulin). 5. Alteration of the activity of some enzymes that are involved in glucose metabolism. 6. Slowing down the absorption of carbohydrates from the gut. 36medicinal plants and their products reviewed by Grover and colleagues [11]. They studied hypoglycemic action of the plants. 13altered the activities of hepatic enzymes involved in glucose metabolism (stimulation of glucokinase and glycogen synthase and inhibition of glycogen

phosphorylase and glucose 6-phospatase), 11 stimulated insulin secretion from pancreatic beta cells, 4 decreased intestinal absorption of glucose, 3 increased insulin sensitivity, 3 regenerated or protected pancreatic beta-cells from damage and 2 acted like insulin. Similarly, of the 60 plants extracts reviewed by Bnouham and co-workers [46, 47] whose hypoglycemic mechanism of action have been studied, 20 stimulated insulin secretion from pancreatic beta cells, 11 altered the activities of hepatic enzymes involved in glucose metabolism, 11 decreased the intestinal absorption of glucose, 11increased insulin sensitivity, 4 regenerated or repaired pancreatic beta-cells and 3 acted like insulin. It can be concluded on the basis of the above mentioned reviews that the majority of antidiabetic medicinal plants exert their blood glucose lowering effect through stimulation of insulin release from pancreatic beta cells or through alteration of some hepatic enzymes involved in glucose metabolism. Another point of note in the above mentioned reviews is that a given plant or its product may exert its blood glucose lowering effect through a combination of more than one mechanism [11].

**Investigation of the antidiabetic activity of plant substances.**

To study antidiabetic potential of medicinal plants, Firstly, candidate plants are collected, extracted and screened for hypoglycemic activity using either in vitro or in vivo bioassay techniques. Secondly, active ingredients are isolated and identified from plants showing hypoglycemic effects during the screening tests. Thirdly, the blood glucose lowering mechanism of action of the crude plant extract and active ingredients is investigated. Fourthly, clinical trials are conducted on the crude plant extract or isolated active ingredients [30].

**Monitoring of medicinal plants for antidiabetic activity**

Candidate medicinal plant material (usually selected on the basis of information obtained from traditional healers and herbalist) are collected, dried, powdered and extracted with a suitable solvent (usually either water or alcohol) and screened for hypoglycemic activity. Screening tests commonly used to assess the antidiabetic/hypoglycemic activity of medicinal plants.

**In vivo bioassay**

In vivo bioassay screening tests for antidiabetic activity of medicinal plant extracts and other antidiabetic remedies are usually carried out in normal or diabetic animals in which diabetes has been induced either by chemical, dietary, surgical or genetic manipulations [49, 50] [51, 52]. By far the most commonly used animal models for screening plants for antidiabetic activity are the chemically (alloxan and streptozotocin) induced diabetic animal models [52]. Alloxan and streptozotocin exert their diabetogenic action when administered parenterally: intravenously, intraperitoneally or subcutaneously [52]. The dose of these agents required for inducing diabetes depends on the animal species, route of administration and nutritional status. According to the administered dose of these agents, syndromes similar to type 2 diabetes mellitus or glucose intolerance can be induced [53, 54]. In general, the majority of published studies which evaluated the antidiabetic activity of medicinal plants using alloxan or streptozotocin-induced animal models of diabetes report the amount of reduction of blood glucose that is always evaluated after a period of fasting following acute or chronic treatment with a specific natural product [11]. Comparative studies are carried out with non-diabetic and/or diabetic animal groups treated with known antidiabetic drugs. Glucose is measured by standard glucose-oxidase or dehydrogenase assays, mainly by means of commercial meters available everywhere [52, 55]. Animal models of diabetes appear to be more useful in screening plants for their antidiabetic activity than in vitro bioassay screening techniques, but ethical and practical considerations make it impossible to screen large numbers of samples [52].

**In vitro cell based assays**

Cell based assays commonly used to screen or evaluate the antidiabetic activity of medicinal plants belongs to a class of in vitro bioassays known as “mechanism based assay” [56, 57]. A mechanism-based bioassay differ from an ordinary cell culture bioassay in that it can provide a possible mechanism of action at the same time that the plant material is screened for biological activity[57]. Two different types of mechanism based in vitro bioassays are commonly used to assess the antidiabetic/hypoglycemic of medicinal plants and/or products: the insulin secretion stimulation [58, 59] and the glucose uptake biosasays [57] [60].

**Insulin secretion stimulation bioassays**

Insulin secretion stimulation bioassays in general, assess the ability of a plant extract or natural product to stimulate perfused pancreas, isolated pancreatic islets cells or clonal pancreatic beta cell–lines (e.g. BRIN-BD11 cells) to secrete insulin [61, 62] In a typical insulin secretion stimulation bioassay cells are seeded (at a specified density) usually in 24- or 96-microtitre well plates, and cultured overnight in a suitable buffer supplemented with glucose, 10%

foetal calf serum and antibiotics. Following attachment of cell to the plates, cultured cells are washed several times and incubated in Krebs ringer buffer (KRB) containing 1 mM glucose in the presence or absence of plant extracts and other test agents. Positive and negative controls are also included in the well plates. Following incubation, aliquots are removed from each well, centrifuged and assayed for insulin levels [61]. Plants whose antidiabetic mechanism of action has been evaluated this way include Medicago sativa.

**Glucose uptake bioassays**

These types of bioassays assess the ability of plant materials to enhance glucose uptake by insulin target cell-lines (e.g. C2C12 myocytes, 3T3-L1 preadipocytes and human Chang liver cells) [56, 63] [60]. A glucose uptake bioassay is generally performed by incubating cultured insulin target cells in a buffer containing glucose (radiolabeled (tritiated 2-deoxyglucose) or unlabelled) and insulin in the presence and absence of the candidate plant extract [57]. Following incubation, glucose in aliquots of the incubation media is measured by means of a scintillation counter or colorimetrically [64]. The difference between the initial and final glucose concentration equals the amount of glucose taken up by the cultured cells and provides a measure of the antidiabetic activity of the plant extract under evaluation [65] [60]. As with other cell based in vitro bioassays, mechanism based bioassays for the assessment of the antidiabetic activity of medicinal plants are generally faster and uses relatively small amounts of materials than the in vivo bioassays. However, antidiabetic/hypoglycemic activity might be missed, for example, where a metabolite rather than the parent substance is the active component [65]. Another disadvantage of these techniques is that only "acute" or immediate effects are measured, whilst effects that may only be apparent after chronic exposure to the antidiabetic compound are overlooked [65].

**Sub-molecular enzyme inhibition-based assays**

Some antidiabetic agents are known to exert their blood glucose lowering effects through inhibition of specific carbohydrate metabolizing enzymes. For this reason several researchers [66, 67] have investigated the ability of plant extracts to inhibit the activities of enzymes such as α-amylase, α-glucosidase, hexokinase (glucokinase) and glucose 6-phosphatase by means of in vitro sub-molecular enzyme inhibition assays. A typical in vitro enzyme inhibition based assay involves three distinct steps. Firstly, the enzyme is pre-incubated in an appropriate buffered solution with or without the test compound. In addition to the incubation buffer, the test solution may include numerous other reagents such as sulfhydryl compounds, metals, protein cofactors and stabilizing agents that are needed by the enzyme. This pre-incubation step allows a maximum opportunity for the enzyme to interact with the test substance before the reaction is initiated. The second stage is the initiation of the reaction. This is most often done by automated or manual addition of substrate to each tube or well. Finally, the reaction must be terminated if it is single-time point readout and the amount of the product formed or the loss of the substrate must be determined. Stopping the reaction can be achieved by a variety of ways depending upon the particular enzyme. One general way is to denature the enzyme by addition of a denaturing agent, for example trichloroacetic acid or a rapid increase in temperature. If a metal ion is required for the activity of the enzyme, the reaction may be stopped by addition of a chelating agent such as EDTA to sequester the metal ion. Once the reaction is stopped, absorption readings are made against a blank by means of a spectrophotometer.

**Investigation of the mechanism of action of antidiabetic plant extracts**

As described an antidiabetic agent may exert its blood glucose lowering effect by stimulating insulin secretion from pancreatic beta-cells, enhancing glucose uptake by fat and muscle cells, altering the activity of some enzymes that are involved in glucose metabolism or slowing down the absorption of sugars from the gut [29, 47, 68, 69].

**Effect on insulin secretion**

In most published studies, investigation of the effect of medicinal plant extract on insulin secretion in vivo has involved the use of streptozotocin or alloxan induced animal models of diabetes [70] [5, 6, 71, 72]. Both alloxan and streptozotocin causes destruction of pancreatic beta cells resulting in reduced insulin secretion [52, 73]. In streptozotocin and alloxan induced animal models of diabetes, insulin is markedly depleted but not absent [52, 74, 75]. For this reasons these animal models have been widely used to study the effect of antidiabetic remedies on insulin secretion in vivo.

In order to investigate the effect of a plant extract on insulin secretion in vivo, the majority of published studies have divided normal animal and diabetic animals into at least five groups: normal control rats, normal rats treated with plant extract, diabetic control; diabetic rats treated with plant extract and diabetic rats treated with a conventional insulin secretory [5, 71, 76, 77]. Experimental animals are then treated with the plant extract for a given period of time while

control groups receive vehicle during the experimental period. At the end of the experimental period blood is withdrawn for the measurement of plasma insulin. A significant increase in the plasma insulin level of experimental rats compared to those of control rats would suggest the insulinotropic effect of the plant extract, whereas a significant increase in the plasma insulin level of extract treated diabetic animal compared with the diabetic control but no difference between the plasma levels of extract treated normal animal and normal control would suggest a regenerative effect of the plant extract on pancreatic beta cells [46, 47, 71, 78-79].

**Inhibition or activation of carbohydrate metabolizing enzymes**

It has been establish that some antidiabetic remedies, for example, metformin exert its blood glucose effects by inhibiting endogenous glucose production by the liver through the process of gluconeogenesis and glycogenolysis [79-80]. For this reason, as part of efforts to find out the possible mode of action of antidiabetic remedies, several researchers have investigated the effect of plant extracts on the activities of gluconeogenic enzymes: glucose 6-phosphatase, fructose 1,6-bisphosphatase; the glycogenolytic enzyme; glycogen phosphorylase and hepatic glucokinase. In order to investigate the effect of medicinal plant extract on key enzymes involved in glucose homeostasis in vivo, the study design used are similar to the one describe above for the study the effect of plant extract on stimulation of insulin except that at the end of the feeding period blood and selected tissues are also collected for the measurement of the activity of selected enzymes in plasma or tissue homogenates in vitro [69, 81, 82].

**Conclusion:**

Diabetes is one of the most prevalent chronic diseases throughout the world, affecting more than 300million people worldwide. For this, therapies developed along the principles of western medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. Herbs are used to manage diabetes and their complications. Therefore, treating diabetes mellitus with plant derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. In this review article, hypoglycemic mechanism of medicinal plants was considered. Scientists working the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure different kinds of diabetes in man and animals. Isolation & identification of active constituents of plants, preparation of standardized dose & dosage regimen can play a significant role in improving the hypoglycemic action. Herbal therapy for diabetes has been followed all over the World successfully. Herbs are used to manage diabetes and their complications. A large number of plants, screened for their anti diabetic effect, have yielded certain interesting leads as mentioned above, however more laboratorial work is needed to specify the mechanism of medicinal plant and their anti diabetic actions.

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