# FEATURE ARTICLE

## Mechanism of Action of Natural Products Used in the Treatment of Diabetes Mellitus

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**ABSTRACT** Diabetes mellitus (DM) is a metabolic disorder caused because of insufficient or inefficient insulin secretary response and it is characterized by increased blood glucose levels (hyperglycemia). DM is a heterogonous group of syndromes. Glucose is the main energy source for the body, and in the case of DM, management of glucose becomes irregular. There are three key defects in the onset of hyperglycemia in DM, namely increased hepatic glucose production, diminished insulin secretion, and impaired insulin action. Conventional drugs treat diabetes by improving insulin sensitivity, increasing insulin production and/or decreasing the amount of glucose in blood. This article provides a comprehensive review of the mode of action of most popular hypoglycemic herbs, such as ginseng, bitter melon, fenugreek, banaba, gymnema and *Coptis chinensis*. The herbs act by increasing insulin secretion, enhancing glucose uptake by adipose and skeletal muscle tissues, inhibiting intestinal glucose absorption and inhibiting hepatic glucose production. Although evidence from animals and humans consistently supports the therapeutic effect of these phytomedicines, multi-centric large-scale clinical trials have not been conducted to evaluate the safety and efficacy of these herbal medicines and their interaction with conventional drugs when both are administered simultaneously.

**KEYWORDS** hyperglycemia, medicinal plants, ginseng, bitter melon, fenugreek, banaba

Diabetes mellitus (DM) is a chronic disease caused by inherited and/or acquired deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin that is produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damages many of the body's systems, in particular the blood vessels and nerves. DM is a metabolic disorder and abnormally high blood glucose levels (hyperglycemia).[1] DM can be divided into two major categories insulin dependent diabetes mellitus (IDDM) or type 1 (an autoimmune disease of younger patients with a lack of insulin production causing hyperglycemia and a tendency towards ketosis) and noninsulin-dependent diabetes mellitus (NIDDM) or type 2 (a metabolic disorder resulting from the body's inability to produce enough or properly utilize insulin hence patients have hyperglycemia but are ketosis resistant). Over 90% of patients with diabetes have type 2. Currently, an estimated 170 million people worldwide suffer from DM and it is predicted that this number will double by the year 2030.[2-4] The reasons for this global rise are[5] growth of aged population, increasing trends towards obesity, unhealthy diet, and sedentary lifestyle.[6] This condition requires medical treatment and a number of lifestyle changes.

Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of DM. Plants have been used traditionally throughout the world because of their effectiveness, less side effects and relatively low cost.[7] Therefore, investigation on such agents from traditional medicinal plants has become more important. Humankind has a long history in the use of herbal medicines. Well-known Ayurvedic physicians Maharshi Charaka (600 BC) and Sushruta (400 BC) correctly described almost all the symptoms of this disease.[8] India and China have a rich history of using various potent herbs and herbal components for treating diabetes. Many Indian and Chinese


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plants have been investigated for their beneficial use in different types of diabetes and are reported in numerous scientific journals.

Today the management of diabetes without any side effect is still a challenge to the medical fraternity. Wide array of plant derived active principles have demonstrated antidiabetic activity. The main active constituents of these plants include alkaloids, glycosides, galactomannan gum, polysaccharides, peptidoglycan, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids and inorganic ions.[9] These affect various metabolic cascades, which directly or indirectly affect the level of glucose in the human body. This review article highlights the current researches on the efficacy, side effects and mechanism of action of phytochemicals and herbs used in the treatment of diabetes. Previous work, which has been published in non-indexed and obscure journals, may have been missed out in this review as citations for the present article were predominantly taken from Diabetes Medicinal Plant Database (DiaMedBase) (http://www.progenebio.in/DMP/DMP.htm).

## 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. There are several types of glucose-lowering drugs, including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones) and $\alpha$-glucosidase inhibitors (miglitol, acarbose).[10] New peptide analogs, such as exenatide, liraglutide and dipeptidyl peptidase (DPP)-4 inhibitors, increase glucagon iike peptide (GLP-1) serum concentration and slow down the gastric emptying.[11,12] Most glucose-lowering drugs, may have side effects, including severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness and even death (Table 1).

The mechanism of insulin release from $\beta$-cells in response to changes in blood glucose concentration is a complex process (Figure 1). Initially some glucose enters the $\beta$-cells with the help of glucose transporter 2 (GLUT2), which is phosphorylated by the enzyme glucokinase enzyme. This modified glucose is further metabolized to produce adenosine-triphosphate (ATP). The increase in ATP: adenosine-diphosphate (ADP) ratio causes the closure of ATP-gated potassium channels in the cell membrane thereby preventing the passage of potassium ions. Due to this change there is a rise in the internal positive charge of the cell causing its depolarization. The net effect is the activation of voltage-gated calcium channels, which transports calcium ions into the cell. The increase in intracellular calcium concentration triggers the export of the insulin stored granules (by a process known as exocytosis) from $\beta$-cells into the nearby blood vessels.[13] The insulin stimulation followed by cascade signaling enhances glucose intake, utilization and storage in various tissues. In diabetic patients, the body loses insulin producing capacity as a result

**Table 1. Existing Synthetic Drugs for Type2 DM in Market and Their Molecular Targets, Site of Action and Adverse Reactions**

| Drug class | Molecular target | Site of action | Adverse reaction |
|---|---|---|---|
| Insulin | Insulin receptor | Liver, muscle, fat | Hypoglycemia, weight gain |
| Sulphonylureas | SU receptor, $K^+$ ATP Channel | Pancreatic $\beta$-cells | Hypoglycemia, weight gain |
| Biguanides | Not clear | Liver, muscle | Gastrointestinal disturbance, lactic acidosis |
| Acarbose, milglitol | $\alpha$-glucosidase | Intestine | Gastrointestinal disturbance |
| Thiazolidinedione | PPAR-$\gamma$ | Fat, muscle, liver | Weight gain, edema, anemia |
| Exenatide | GLP-1 receptor | Pancreatic $\alpha$-cells, intestinal mucosa-L cells | Nausea, hypoglycemia, diarrhea |
| Pramlintide | Amylin receptors | Nucleus accumbens, dorsal vagal complex | Nausea, hypoglycemia |
| Sitagliptin | DPP-4 | Intestine | Headache, nausea |
| Repaglinide | $K^+$ ATP channel | Pancreatic $\beta$-cells | Hypoglycemia, bellyache, nausea, liver damage |

Notes: SU: sulphonylurea; ATP: adenosine-diphosphate; PPAR: peroxisome proliferator-activated receptor

of pancreatic β-cell apoptosis or insulin insensitivity. The cytokines, lipotoxicity and glucotoxicity are three major stimuli for β-cell apoptosis.[14]

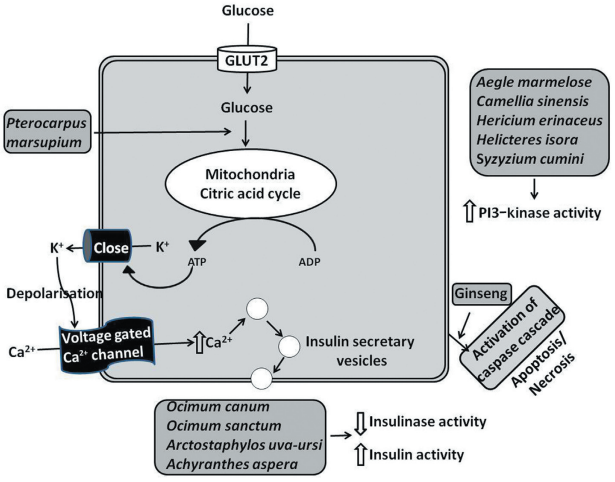


**Figure 1. Effects of Phytochemicals in Insulin Secretion and Pancreatic-β-cell Apoptosis**

Notes: ⇧ - upregulation; ⇩ - downregulation, the same below

## Medicinal Plants: A Safe Tool to Manage DM

Management of diabetes without any side effects is still a challenge to the medical fraternity.[15] World ethnobotanical information about medicinal plants reports that about 800 plants are used in the control of DM. There are around 450 experimentally proven medicinal plants having antidiabetic properties but complete mechanism of action is available only for about 109 of them.[8]

The traditional medicinal plants with various active principles and properties have been used since ancient time by physicians and laymen to treat a great variety of human diseases including diabetes, coronary heart disease, and cancer.[16] India and China have a long history of use of medicinal plants for the management of diabetes. Charaka and Sushruta described in their Charaka samhita and Sushruta samhita the phytopharmacological aspects of diabetes and its complications.[17] Medicinal plants have beneficial multiple activities including manipulating the carbohydrate metabolism by various mechanisms, preventing and restoring integrity and functioning of β-cells, insulin releasing activity, improving glucose uptake and utilization, and antioxidant properties.

The market for herbal medicines is booming and evidence for their effectiveness is growing, but it is also being counterbalanced by inadequate regulation. Therefore product standardization, efficacy, safety and therapeutic risk/benefits associated with the use of herbal medicines need proper evaluation. A detailed clinical investigation to confirm the mechanism of action is also absolutely necessary.[18] However, a few herbal medicines have been well characterized and their efficacy has been demonstrated in systematic clinical trials, similar to commercially available synthetic drugs.

Herbal products have been thought to be inherently safe, because of their natural origin and traditional use rather than on systemic studies designed to detect adverse effects (AEs).[19] AEs from herbal remedies are not rare, but their frequency and severity are unknown. To overcome these drawbacks the scientific studies of herbal remedies and their potential to cause interactions on concomitant use with conventional medicines need to be systematically studied.[20] Some of the most commonly used synthetic drugs and medicinal plants with their target tissues/ organs and their modes of action to manage blood glucose levels are shown in Table 2.

## Mechanism of Action of Commonly Used Medicinal Plants

There are over 170 different natural medicines used for combating diabetes. Also thousands of dietary supplements are commercially marketed for people with diabetes. However, only a fraction of these products have reliable clinical evidence of effectiveness. The phytochemicals are working through various metabolic pathways which involve glucose or its derivatives as substrate or as product. They affect glucose metabolism (glycolysis, Kreb's cycle), pentose phosphate pathways, glycogenesis, glycogenolysis, gluconeogenesis, absorption of glucose via alimentary canal and increase the insulin release, its production and its efficacy.[13] Many of these natural medicines modulate blood sugar levels through a variety of mechanisms. In some cases their effects are similar to conventional medicines (Table 2). These results are subject to several factors. Each herb consists of various components, only a few of which may be therapeutically effective (Reference). Different parts of an herb will have different ingredient profiles. Different extraction methods may yield different active ingredients. Herbal formulae containing multiple herbs may have synergistic effects.[21,22] In this review some of the most common medicinal plants are discussed

**Table 2. Commonly Used Conventional and Natural Medicines for Diabetes**

| Categories | Target tissue and mode of action | Conventional drugs | Natural medicines |
|---|---|---|---|
| Hypoglycemic agents | Pancreas (Increase insulin secretion) | Sulphonylurea, miglitinides | Banaba (*Lagerstroemia speciosa*)<br>Bitter melon (*Momordica charantia*)<br>Fenugreek (*Trigonella foenum-graecum*)<br>Gymnema (*Gymnema sylvestre*) |
| Insulin sensitizers | Liver (Decrease glucose production);<br>Adipose tissue and skeletal muscles (Increase peripheral glucose uptake) | Metformin, thiazolidinedione | Agaricus mushroom (*Agaricus blazei*)<br>American ginseng (*Panax quinquefolius*)<br>Banaba (*Lagerstroemia speciosa*)<br>Cassia cinnamon (*Cinnamomum aromaticum*)<br>*Panax ginseng*<br>Prickly pear cactus (*Opuntia ficus-indica*)<br>Soy (*Glycine max*)<br>Vanadium |
| Carbohydrate absorption inhibitors | Intestine (Decrease glucose absorption) | α -glucosidase inhibitor | Bean pod (*Phaseolus vulgaris*)<br>Blond psyllium (*Plantago ovata*)<br>Fenugreek (*Trigonella foenum-graecum*)<br>Glucomannan (*Amorphophallus konjac*)<br>Guar gum (*Cyamopsis tetragonoloba*)<br>Oat bran (*Avena sativa*)<br>Prickly pear cactus (*Opuntia ficus-indica*)<br>Soy (*Glycine max*)<br>White mulberry (*Morus alba*) |
| Miscellaneous | | Exenatide (Byetta),<br>Pramlintide (Symlin),<br>Saxagliptin (Onglyza),<br>Sitagliptin (Januvia) | Alpha-lipoic acid<br>Chia (*Salvia hispanica*)<br>Coenzyme Q10<br>Selenium<br>Stevia (*Stevia rebaudiana*) |

with their antidiabetic properties and their mechanism of action.

## Ginseng

This is the most studied medicinal plant for its hypoglycemic activities. The medicinal and its efficacy potency of ginseng mainly depend on its geographical locality, dosage, processing and types of diabetes. *Panax ginseng* also known as Chinese or Korean ginseng has the highest therapeutic potency. *Panax quinquefolius,* i.e., American ginseng has medium potency, while *Panax japonicus* (Japanese ginseng) is considered to have low potency. The most commonly used therapeutic ginseng is *Panax ginseng* because of its highest effectiveness. Ginseng is able to decrease blood glucose by affecting various pathways (Figure 2).

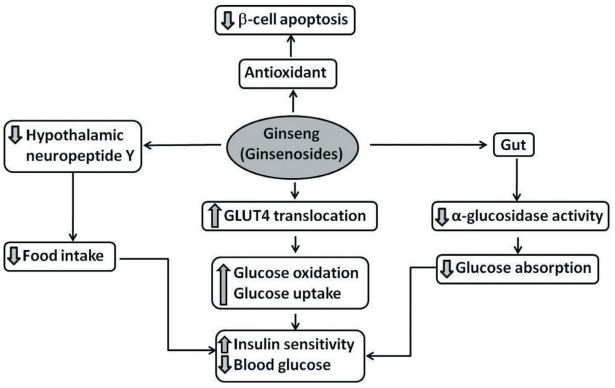


**Figure 2. Mechanism of Action of Ginseng to Improve Glucose Metabolism**

Korean red ginseng (0.1–1.0 g/mL) significantly stimulates insulin release from isolated rat pancreatic islets at a glucose concentration of 3.3 mmol/L.[23] The treatment with oral administration of heat-processed American ginseng (H-AG) at a dose of 100 mg/kg of body weight for 20 days decreased serum levels of glucose, glycosylated proteins and hemoglobin $A_{1c}$ ($HbA_{1c}$) in streptozotocin (STZ)-induced diabetic rats. The treatment also improved the decreased creatinine clearance levels and decreased the accumulation of N ( ε )-(carboxymethyl) lysine and its receptors in kidney.[24] *Radix Ginseng Alba* improved hyperglycemia in KKAy mice, possibly by blocking the intestinal glucose absorption and inhibiting the hepatic glucose-6-phosphatase. *Radix Ginseng Palva* has a similar effect through the up-regulation of adipocytic PPAR-y protein expression and inhibiting the intestinal glucose absorption.[25] Clinical trials show that taking 3 g of American ginseng 2 h before a meal reduces the postprandial blood glucose.[26] A total of 705 components have been isolated from ginseng, including ginsenosides, polysaccharides, peptides and

polyacetylenic alcohols, among which ginsenosides are believed to be responsible for its efficacy.[27] Fat-soluble components have more hypoglycemic activity than the water-soluble extract of the ginseng root. *Panax ginseng* and American ginseng, both contain ginsenosides, which are thought to decrease the insulin resistance and improve insulin sensitivity. Some products with low levels of ginsenosides content do not seem to be beneficial for lowering the blood glucose levels.[28]

*Panax quinquefolius* (10 mg/1 kg diet) increases body weight and decreases cholesterol levels, PPAR actions and triglyceride metabolism in male Zucker diabetic fatty (ZDF) rats with type 2 DM.[29] Human clinical trials with, *P. quinquefolius improves* post-prandial glycemia in patients with type 2 DM.[30] Ginsenoside Rh2 decreases plasma glucose concentrations within 60 min in a dose-dependent manner in rats fed with fructose rich chow and after single intravenous injection in STZ-induced insulin resistant rats.[31] The ginsenoside Rh2 might be acting through the release of Acetyl-choline (ACh) from nerve terminals which stimulate muscarinic M(3) receptors in pancreatic cells to increase insulin secretion.[32] It is also effective in the treatment of type 1 DM. At a concentration of 0.1–1.0 mg/mL ginsenosides inhibit cytokine-induced apoptosis of β-cells. The mechanism of action may be through the reduction of nitric oxide (NO), production of reactive oxygen species (ROS),[24] inhibition of p53/p21 expression and inhibition of cleavage of caspases and poly (ADP-ribose) polymerase (PARP).[33]

The major side-effects of ginseng include insomnia, diarrhea, vaginal bleeding, breast pain, severe headache, schizophrenia and fatal Stevens-Johnson syndrome.[34] 1–3 g of root or 200–600 mg of extract is the safe recommended dosage of ginseng.[26] Although ginseng products look promising for treating diabetes, more evidence is needed about their long-term effectiveness and safety.

### Bitter Melon (Bitter Gourd, Karolla, *Momordica Charantia*)

It is a popular vegetable as well as an herb in China. Bitter melon has been used as an herb for at least 600 years in South China. Hypoglycemic effects of bitter melon were demonstrated in cell culture, animal models[35] and human studies.[36] The antidiabetic components in bitter melon include charantin, vicine, polypeptide-p, alkaloids, and other non-specific bioactive anti-oxidants. A hypoglycemic peptide, polypeptide-p, has been isolated from fruits, seeds, and tissue of *Momordica charantia* Linn. (bitter gourd) and the amino acid analysis indicated a minimum molecular weight of approximately 11 000 (166 residues). The major components in methanol extract of bitter melon include 5-β, 19-epoxy-3-β,25-dihydroxycucurbita-6,23(E)-diene and 3-β,7-β,25-trihydroxycucurbita-5,23(E)-dien-19-al. They showed hypoglycemic effects at 400 mg/kg in diabetic male ddY mice.[37] Oleanolic acid glycosides, isolated from bitter melon, improved glucose tolerance in type 2 DM by preventing sugar from being absorbed in intestines. In STZ-induced diabetic mice, bitter melon was able to decrease the blood glucose via suppression of STZ-induced peroxidation and apoptosis in β-cells, by increasing the glycogen content in liver and muscle, and activating hepatic glucokinase, hexokinase, and phosphofructokinase.[38] In STZ induced diabetic rats gluconeogenesis was inhibited through downregulation of the activities of hepatic glucose-6-phosphatase and fructose-1,6-bisphosphatase and enhancement of glucose oxidation by upregulation of glucose-6-phosphate dehydrogenase (G6PDH) in red cells and hepatocytes.[39] Ethyl acetate (EA) extract of bitter melon activates PPARs α and γ,[40,41] modulates the phosphorylation of IR and its downstream signaling pathway, thereby lowering the plasma apoB-100 and apoB-48 in mice fed with high-fat diet. The momordicosides (Q, R, S and T) stimulate the GLUT4 translocation to the cell membrane and increase the activity of adenosine monophosphate (AMP)-activated protein kinase (AMPK) in L6 myotubes and 3T3-L1 adipocytes, thereby enhancing the fatty acid oxidation and glucose disposal during glucose tolerance tests in both insulin-sensitive and insulin-insensitive mice.[42]

Reported AEs of bitter melon include hypoglycemic coma, convulsions in children, reduced fertility in mice, a favism-like syndrome, increased activities of γ-glutamyl transferase and alkaline phosphotase in animals and headaches in humans. Bitter melon has an additive effect with other glucose-lowering agents.[43] Bitter melon also reduces adiposity in rats fed with high-fat diet.[44]

In summary, bitter melon has some activities in

the regulation of glucose and lipid metabolism (Figure 3), which were tested in animals and patients. The mechanism of action remains to be fully established. Bitter melon can be used as a dietary supplement herbal medicine for the management of diabetes and/or metabolic syndromes.[45] The therapeutic efficacy of bitter melon needs to be evaluated in the clinical trials with large sample size.

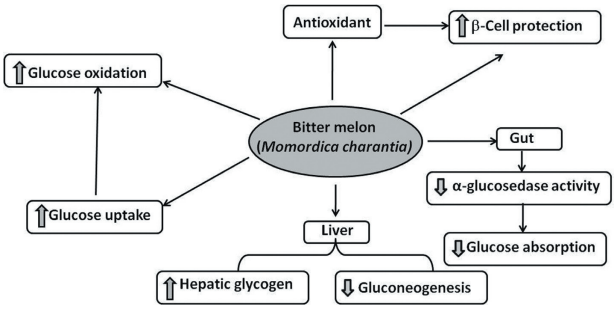


**Figure 3. Mechanism of Action of Bitter Melon in the Reduction of Blood Glucose**

*Coptis Chinensis*

*Coptis chinensis* is commonly used to treat diabetes in China. Berberine is an isoquinoline alkaloid and the active ingredient present in *Coptis chinensis*. It is found in plant roots, rhizomes, stems, and barks.

Intragastric administration of berberine (100 and 200 mg/kg) in diabetic rats decreased fasting blood glucose levels and total cholesterol, triglyceride and low-density lipoprotein cholesterol (LDL-C) in the serum whereas increased high-density lipoprotein cholesterol (HDL-C) and NO level, and blocked the increment of superoxidase dismutase (SOD) and glutathione peroxidase (GSH-px) levels.[46] Multiple mechanisms may be responsible for the weight reduction and increased insulin response induced by berberine. It increases GLUT4 translocation in adipocytes and myotubes,[47] increases AMPK activity, decreases glucose-stimulated insulin secretion (GSIS) and palmitate-potential insulin secretion in MIN6 cells and rat islets.[48] It also increases the expressions of PPAR $\alpha$ / $\delta$ / $\gamma$ proteins in liver,[49] increases the expressions of insulin receptor in liver and skeletal muscle cells and improves cellular glucose consumption in the presence of insulin.[50] Berberine also decreases significantly the activity of intestinal disaccharidases and $\beta$-glucuronidase in STZ-induced diabetic rats.[51] Dihydroberberine (dhBBR), a berberine derivative, demonstrated *in vivo* beneficial effects in rodents fed with high-fat.[52]

Studies showed that berberine restored damaged pancreas tissues in diabetic rats induced by alloxan.[51] Berberine improves renal dysfunction in rats with diabetic nephropathy by controlling the blood glucose, reducing the oxidative stress and suppressing the polyol pathway.[51] Berberine ameliorates renal injury in STZ-induced diabetes, neither by suppression of oxidative stress nor by inhibition of aldose reductase activity but through some unknown mechanism.[51] Berberine is found to lower fasting blood glucose and postprandial blood glucose in 48 adult patients with type 2 diabetes.[53,54] The hypoglycemic effect of berberine in clinical studies in 36 adult patients with type 2 diabetes was similar to that of metformin.[54] The fasting plasma insulin, insulin insensitivity index, the total cholesterol and LDL-C reduced significantly.[54] The different modes of actions of berberine in lowering the blood glucose level are summarized in Fgure 4.

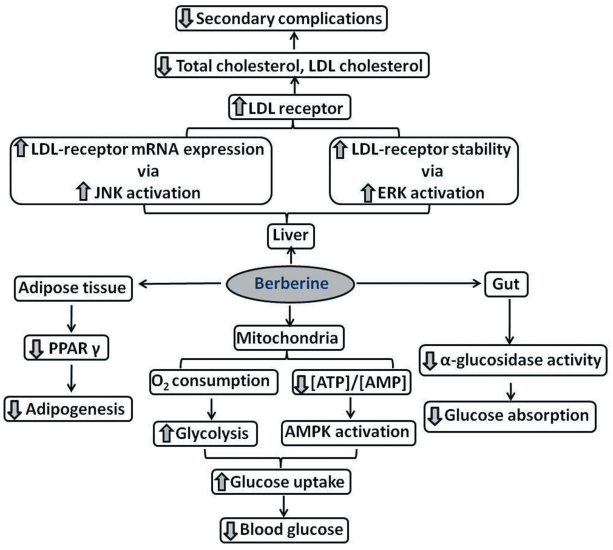


**Figure 4. Mechanism of Action of Berberine in Blood Glucose Regulation**

Notes: JNK: c-Jun N-terminal kinase; ERK: extracellular signal regulated kinase

Banaba (*Lagerstroemia Speciosa*)

Banaba is the name for a species of crepe myrtle. Extracts of the banaba leaves are very popular in the Philippines and Southeast Asia. It is commonly used by diabetes patients in North America. Banaba contains two important constituents and has two important effects on diabetic patients. Banaba extracts containing corosolic acid and ellagitannins seem to have an insulin-like effect and also activate insulin receptors.[55] The latter activity is thought

to be secondary to the activation of the insulin receptor tyrosine kinase or the inhibition of tyrosine phosphatase. Preliminary clinical research shows that type 2 diabetes patients who take a specific banaba extract (glucosol) for 2 weeks have on an average 10% lower blood glucose levels, than patients receiving placebo.[55] Although there are evidences regarding the hypoglycemic effect of banaba, their long term effects need to be researched.

Fenugreek (*Trigonella Foenum-Graecum*)

Fenugreek is an herbal remedy sourced from the dried seeds of a plant native to India, China and North Africa. It has long been used in Ayurveda as a laxative and demulcent (a substance that soothes irritation of the skin, mouth, nose, or throat). Studies with mice indicate that 4-hydroxyisoleucine (an amino acid derived from fenugreek) may help to stimulate the secretion of insulin, reduce insulin resistance, and decrease blood sugar levels. There is very limited human-based evidence to support the use of fenugreek in diabetes management.[56] Preliminary research shows that type 2 diabetes patients who mix 15 g of ground, powdered fenugreek seeds with a meal have lower postprandial glucose levels when compared to control.[57] This might be due to a bulk laxative effect and also slowing of carbohydrate absorption from the gastrointestinal tract. But fenugreek also seems to enhance insulin release due to the presence of 4-isoleucine in it.[58] Studies show that adjunct use of fenugreek seeds improves glycemic control and decreases insulin resistance in mild type 2 diabetic patients. There is also a favorable effect on hypertriglyceridemia and improvement in the HDL-C levels. Supplementation with fenugreek leaves improves body weight and liver glycogen and has a significant effect of carbohydrate metabolism similar to glibenclamide.[59]

Fenugreek and sodium orthovandate alone or in low dose combination have been shown to effectively control ocular histopathological and biochemical abnormalities associated with diabetic retinopathy.[60] Low doses of vandate and fenugreek in combination normalizes altered membrane linked functions and GLU4 distribution without any side effects.[61,62] Fenugreek leaf powder reduces oxidative stress in experimental diabetes. Fenugreek supplementation lowers lipid peroxidation and significantly increases antioxidant system in diabetic rats.[63] Fenugreek seeds are rich in protein and contain the unique free amino acid 4-hydoxyisoleucine (4-OH-Ile), which has been characterized as one of the active ingredients for blood glucose control.[64]

When eaten or taken in capsule form, fenugreek may cause gas, bloating, or diarrhea. It may also cause irritation when applied to the skin, may increase the potency of certain medications (such as blood-thinning drugs) and interact with hormonal agents.

Gymnema

Gymnema is an Indian plant referred to as "gurmar" in Hindi, which means "sugar destroying". Gymnema has been tested as a hypoglycemic agent in combination with insulin and the results are encouraging. Preliminary research shows that taking 200 mg/d of gymnema extract cuts the required insulin dose by half and lowers $HbA_{1c}$, in both type 1 and type 2 diabetes. It also increases the number of beta cells in the pancreas and so the internal production of insulin. When 400 mg of this extract is taken with conventional hypoglycemic drug, such as glyburide or tolbutamide, a few patients are able to reduce the dose of the drug or even discontinue it.[65,66] The plant extract seems to work by increasing the endogenous insulin production or by increasing the serum C-peptide levels. 45C-peptide is a chain of amino acids that is cleaved from the proinsulin molecule released by the pancreas to form insulin. Therefore, C-peptide is used as a marker to monitor the release of endogenous insulin. Gymnema also decreases the total cholesterol levels, triglycerides and LDL-C, instead it enhances the levels of HDL-C. The observed behavior may be because gymnema may inhibit the absorption of oleic acid, which is one of the omega-9 fatty acids found in vegetable oil, animal fat, and other sources of dietary fat. The extract might increase the risk of hypoglycemia because it increases insulin production and insulin release, or contain constituents that work like insulin.

Cassia cinnamon

Bark and the flower of this plant have been used for medicinal purposes. In addition to diabetes, Cassia cinnamon is used for gas (flatulence), muscle and stomach spasms, for preventing nausea, vomiting, diarrhea, infections, the common cold, and loss of appetite.[67] It started receiving a lot of attention when a preliminary clinical study suggested

that taking 1-6 g (1 teaspoon = 4.75 g) could lower fasting blood glucose by 18% to 29%.[67] Another clinical trial showed that taking 1 g of a specific Cassia cinnamon product (Cinnamon 500 mg, Puritan's Pride) daily for 90 days significantly reduced HbA1c by about 0.83%.[68] Constituents contained in Cassia cinnamon seem to increase the sensitivity of insulin receptor.[69-71] 1.5 g of Cinnamon cassia powder daily did not significantly reduce fasting plasma glucose, $HbA_{1c}$ or serum lipid profile in type 2 diabetes patients. Other studies also found no significant effect on blood glucose or $HbA_{1c}$.[68,72]

Cassia cinnamon is safe when used in amounts commonly found in foods and in medicinal doses but it is possibly unsafe when taken in large amounts for extended periods, since it contains large amounts of coumarin which may cause or worsen liver disease.

### Agaricus mushroom

Agaricus is originally from Brazil, but has now been commercialized in China, Japan and other Asian countries. It contains polysaccharides including beta-glucans that seem to stimulate markers of immune function and works like immunostimulant similar to other mushrooms.

Agaricus mushroom contains chemicals that might improve the body's use of insulin and decrease insulin resistance in patients with type 2 diabetes. It also seems to increases the levels of adiponectin, which can reduce insulin resistance. Clinical research showed that type 2 diabetes patients who took 500 mg of agaricus mushroom extract three times a day, along with conventional medications, had lower fasting insulin levels when compared to patients who did not take the mushroom.[73] Agaricus mushroom extract seems to be safe for most people when taken for up to 12 weeks but it can cause blood sugar to go too low (hypoglycemia). It can cause itching and liver disease.

## Phytocostituents Having Hypoglycemic Potential

Several phytochemicals including alkaloids, flavonoids, glycosides, glycolipids, polysaccharides, peptidoglycans, carbohydrates, amino acids and saponins[74] (Figure 5) extracted from plant sources have been reported to posses hypoglycemic activity. Several phytochemicals may be found in a single plant and their combined synergistic action may be giving the observed behaviour.

### Alkaloids

Alkaloids are naturally occurring amines and they have pharmacological effects on humans and animals. Resveratrol is a phytoalexin, a class of antibiotic compound produced as part of the plant's defense system.[75] Berberine (Ⅺ) is known to have potent hypoglycemic activity and it is found in *Tinospora cordifolia* (Willd.) Hook. F. & Thomson.[76] Alkaloids including catharanthine (Ⅻ.), vindoline (ⅩⅢ) and vindolinine (ⅩⅣ) isolated from *Catharanthus roseus* (L.) G. Don have been reported to lower blood sugar levels.[77]

### Polysaccharides

Medicinal plants which include *Aloe vera* L., *Ocimum sanctum* L., and *Alpinia galanga* (L.) Willd. contain polysachharides 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.[78]

### 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 *Momordica charantia* L. is reported to posses an insulin-like activity,[79] probably by enhancing the release of insulin and slowing down the glucogenesis. β-sitosterol (ⅩⅥ), a steroid found in *Azadirachta indica* A. Juss.; andrographolide (ⅩⅦ), a diterpenoid lactone, isolated from *Andrographis paniculata* Nees.; [80] and saponin gymnemic acid Ⅳ (ⅩⅧ), isolated from *Gymnema sylvestre* R., exhibit potent hypoglycemic activity in animal models.[81]

### Ferulic Acids

Ferulic acid (4-hydroxy-3-methoxycinnamic acid, ⅩⅨ) 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.[82]

### Flavonoids

Flavonoids are a group of naturally occurring compounds which have hypoglycemic as well as antioxidant properties. They are also a class of

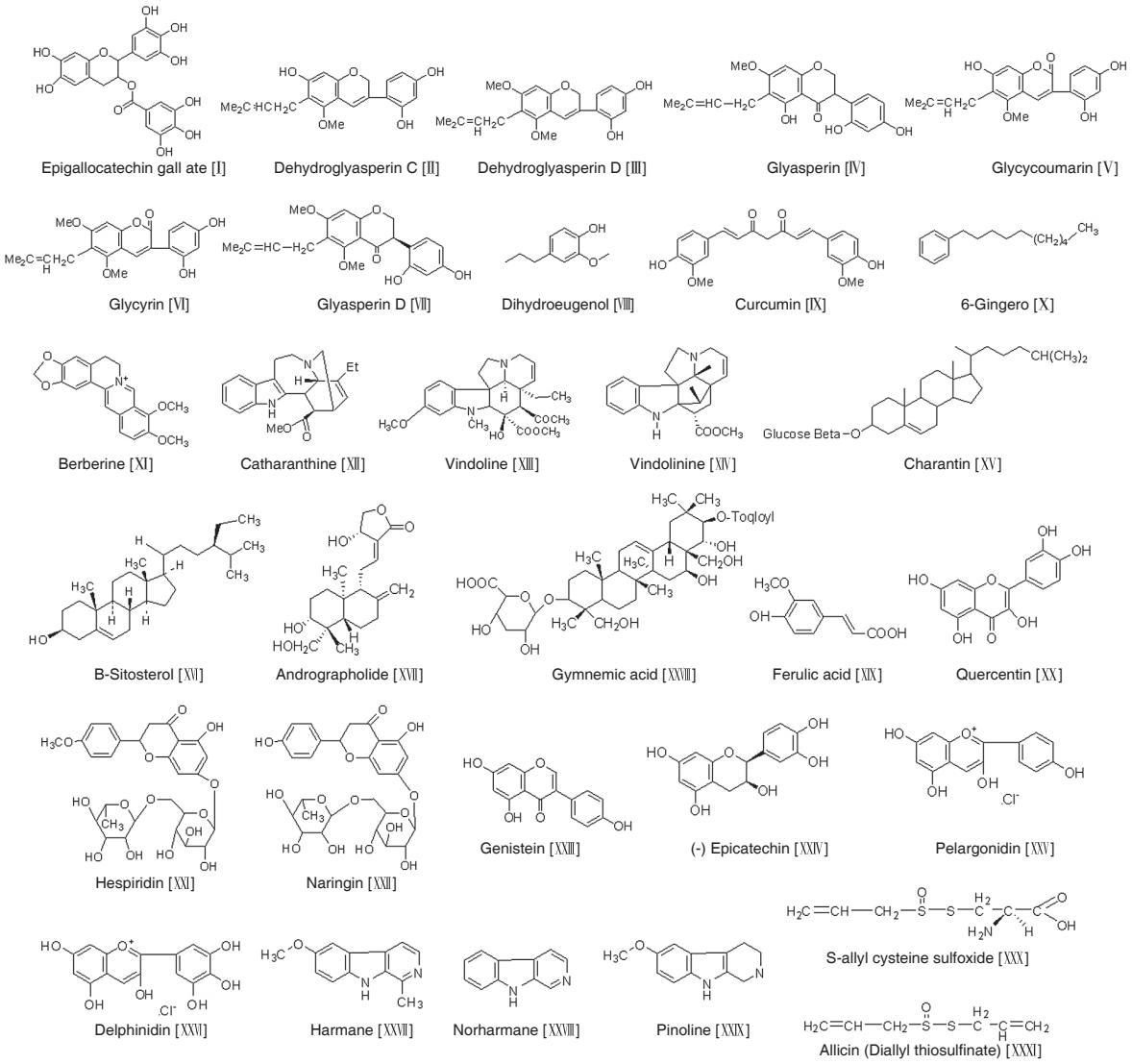


**Figure 5. Phytochemicals Which Induces Hyperglycemia**

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 (ⅩⅩ) is an important flavonoid known to increase hepatic glucokinase activity, probably by enhancing the insulin release from pancreatic islets.[83] It also exerts stimulatory effect on insulin secretion by changing $Ca^{2+}$ concentration.[84] Supplimentation of (0.2 g/kg) hesperidin (ⅩⅪ) or naringin (ⅩⅫ), in the diet of male type Ⅱ diabetes model mice leads to reduction in the blood glucose levels, increase in hepatic glucokinase activity and glycogen concentration. They also lower the activity of hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase and the plasma insulin, C-peptide. 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.[85] Green tea flavonoid, epigallocatechin gallate (Ⅰ), has a glucose-lowering effect in animals. It is reported to decrease the production of hepatic glucose and similar to insulin, increase tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1). It also reduces the expression of phosphoenolpyruvate carboxykinase gene in a phosphoinositide 3-kinase-dependent manner and mimics insulin by increasing PI3K and mitogen-activated protein (MAP) kinase.[86] Another flavonoid, (−)-epicatechin (ⅩⅩⅣ), has been reported to possess insulin-like activity.[87] It acts on erythrocyte membrane-bound acetylcholinesterase in type Ⅱ diabetic patients.[88] Pelargonidin (ⅩⅩⅤ) and delphinidin (ⅩⅩⅥ) also show good hypoglycemic activity.[89]

Imidazoline Compounds

Pancreatic beta cells have imidazoline-Ⅰ binding sites on them. Imidazoline derivatives found in some of the plants have stimulatory action on insulin secretion by activating these binding sites. β-carbolines which include harmane (ⅩⅩⅦ), norharmane (ⅩⅩⅧ) and pinoline (ⅩⅩⅨ), obtained from *Tribulus terrestris* L. are found to increase insulin secretion two- to three-folds in isolated human islets of Langerhans.[90]

Sulfur Containing Compounds

Sulfur containing amino acids namely S-methyl cysteine sulfoxide (ⅩⅩⅨ) and diallyl thiosulfinate isolated from the plants of *Allium sativum* L.[81,92] and *Allium cepa* L.[93,94] activate the enzymes hexokinase, glucose-6-phosphatase, hydroxy-methyl-glutaryl coenzyme A (HMG Co-A) reductase, and lecithin-cholesterol acyltransferase (LCAT) in alloxan induced diabetic rats.

## CONCLUSIONS

Diabetes is a metabolic disorder arising mainly due to the fault in the production of insulin or mounting resistance to its action. In the case of DM, the most serious problem is the side effect which occurs due to the accumulation of glucose. This excess glucose is converted into various compounds and also into free radicals, which damage the vital organs and organelles. There are no specific medicines in the market to treat these complications.

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. Herbal treatments have been used in patients with IDDM, NIDDM, diabetic retinopathy, diabetic peripheral neuropathy, etc. Out of an estimated 250 000 plants, less than 1% have been screened pharmacologically and only a fraction of these for DM. The most commonly used drugs of modern medicine such as aspirin, anti-malarials, anticancers, digitalis etc. originated from plant sources. Therefore, it is prudent to look for options in herbal medicine for diabetes. On the basis of this report which lists the potential effectiveness of medicinal plant against diabetes, it can be assumed that phytochemicals can play a major role in the management of diabetes. This needs further exploration before drugs and nutraceuticals can be developed from these natural resourses. Many herbal therapies have not undergone proper scientific assessment and some have the potential to cause serious toxic effects and major drug-to-drug interaction. Continued research is necessary to elucidate the pharmacological activities of herbal remedies.

The herbs discussed in this paper have shown efficacy in lowering blood glucose in diabetes patients, but the line between whether an herb is a 'drug' or a dietary supplement is unclear. The issues of standardization, characterization, preparation, efficacy, long term side effects and toxicity need to be addressed. Herb-drug interaction and herb-herb interaction is another concern when the phytochemical or herb is taken together with other drugs. Unfortunately, herb-drug interactions in diabetic treatments have not been well documented, except for a few studies.[95,96] A number of supplements are known to have intrinsic effects on serum glucose, for example, ginseng is hypoglycemic in diabetic patients. Gliclazide is an oral hypoglycemic (antidiabetic) classified as a sulfonylurea. St John's Wort increases the apparent clearance of gliclazide significantly. Diabetic patients receiving these at the same time should be closely monitored for possible signs of reduced efficacy. Lowering blood glucose too much could push patients into hypoglycemia. The biggest worry is when natural medicines with hypoglycemic activity, are combined with conventional drugs with similar effects may lead to unexpected harmful reactions.

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