Review of herb supplement use in type 2 diabetes

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Abstract

Diabetes mellitus is a major metabolic disorder and has a big proportion of affliction in the world which is recognized for many complications, as diabetic nephropathy, neuropathy, and retinopathy. Fenugreek, cinnamon, bitter melon, Gymnema Sylvestre, ginger, olive leaf extract, and berberine are the most common plants for treating diabetes. These plants contain many important substances as alkaloids, flavonoids, etc, which are also rich in soluble fibers that help decrease blood sugar by hindering the assimilation and retention of carbohydrates. Fenugreek could improve metabolic symptoms types by bringing down blood glucose and improve glucose tolerance.

Keywords: Fenugreek, cinnamon, bitter melon, Gymnema Sylvestre, ginger, olive leaf extract, berberine, diabetes mellitus

Introduction

Diabetes mellitus (DM) is commonly endocrine disorder and affects more than 400 million people which accounts for 9.1% of the world population. Its prevalence is rapidly increasing and it is estimated that by 2040, 642 million people in the world will be affected by diabetes. DM caused by the reduction of insulin production through the pancreas which results in increase glucose concentrations in blood [1-3].

Diabetes is an inveterate disease that reduces the quality of life, increases the risk of morbidity and mortality, and can damage many of the body systems; particularly the blood vessels and nerves. It is a common and serious metabolic disorder throughout the world [4-6].

Widely structures' ranges of constituent's plant are active hypoglycaemic principles. Ayurveda could use in treating many human diseases. More than 45000 claimed to have been used as medicinal plants in India [7].

The present research aims to review various plant species as fenugreek, cinnamon, bitter melon, Gymnema Sylvestre, ginger, olive leaf extract, and berberine and have used as traditional medicine and have shown hypoglycaemic activity.

Fenugreek (*Trigonella foenum graecum*)

Fenugreek (*Trigonella*)is means "small triangle" related to yellowish-white triangular flower [8]. The name of *Foenum-graecum* (Greek hay) is a native plant in the Mediterranean region (Asia). Fenugreek kinds are known in the world (Table 1). More than 260 species are available in *the Trigonella genus* [9].

Table 1: Fenugreek names (Trigonella foenum graecum) [10].

Language	Common Names
Hindi	Methi, Saag methi, Kasuri methi
English	Fenugreek
French	Fenugreec, Trigonelle
Galician	Alforfa
German	Bockshornklee, Griechisch Heu
Georgian	Solinji, Chaman
Japanese	Koruha, Fenu-guriku
Dutch	Fenugriek
Romanian	Molotru, Molotru comun, Schinduf
Assamese	Methi, Mithi
Sanskrit	Methika

Chemical constituents of fenugreek

Fenugreek seeds are rich sources of soluble dietary fiber [11]. 100 g in seeds give over 65% of daily recommended dietary fiber. Fenugreek contains saponins, hemicelluloses, adhesive, tannins and gelatin, and these mixes help to diminish the

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levels of low-density lipoprotein-cholesterol (LDL) in blood by hindering bile salts reabsorption in the colon [12]. The seed of fenugreek has a high proportion of protein ranging from 20 to 30% as well as an amino acid, 4-hydroxy isoleucine, which potentiates glucose-induced insulin secretion [13]. Fenugreek seed contains a high amount of vitamins like vitamin A, B1, B2 and C (0.003, 0.43, 0.36 and 12 to 43 mg/100g), potassium (603.0 mg/100g), magnesium (42.0 mg/100g), calcium (75.0 mg/100g), zinc (2.4 mg/100g) and iron (25.8 mg/100g) [14]. Fenugreek endosperm contains 35% alkaloids, primarily trigonelline. Flavonoid constitutes more than 100 mg/g of fenugreek seed [15].

Antidiabetic effect of fenugreek

Fenugreek seed extracts have antidiabetic potential by delaying both gastric emptying time and rate of glucose absorption and reduced uptake of glucose is due to the high content of fiber [16]. Pancreatic function tissues protected β cells, elevated serum insulin by β cells regeneration or stimulation of insulin release by the existing β islet cells [17].

Insulin sensitivity, improving insulin action at the cellular level and improved HbA1c level by utilizing glucose in peripheral tissues thereby maintain normal blood glucose level [18].

Free radicals role in diabetes pathogenesis and oxidative stress coexists by reduced antioxidant status as antioxidant activity [18] which could prevent diabetes pathogenesis. Solid-state bioconversion for fenugreek substrate through *Rhizopus oligosporus* shown an increase of natural α-amylase inhibitors associated and increasing phenolic antioxidants and reducing glycemic index. A specific amino acid called 4-hydroxy isoleucine represents about 80% of free amino acid in fenugreek seeds. 4-hydroxy isoleucine reported to suppressing of progression of diabetes 2 in the mice model [19].

Fenugreek oil has antidiabetic effects related to immunomodulatory action and insulation in alloxanized rats. Daily oral by fenugreek steroids showed reducing of glucose blood and improving insulin-immunoreactive β cells [20].

Fenugreek role in diabetes pathogenesis and complications

Important carbohydrate metabolic enzymes were altered in Streptozotocin inducing diabetic rats. Extract of *Trigonella foenum-graecum* and *Psoralea corylifolia* seeds in a compound manner (1:1) recovery activities of liver enzymes and, therefore, they reported that the extract corrected the abnormal metabolism [21].

Diabetic retinopathy and neuropathy both are common complications of diabetes. In one study, fenugreek seeds show and effective in preventing retinopathy [20]. Neuroprotective effects in fenugreek seed powder might result in decreasing in hyperglycemia and oxidative stress, [22].

Cinnamon (Cinnamomum)

Cinnamon is an ancient spice utilized in several cultural practices and using in cooking, furthermore become popular for potential health outcomes because of medicinal effects of cinnamon is declared also its antimicrobial, antioxidant, antitumor, blood pressure-lowering, cholesterol-lowering, and gastroprotective characteristics [23].

Chemical constituents of Cinnamon

Cinnamon has been utilized for centuries as a spice that adds flavor and aroma to food. The chemical composition of cinnamon is as follows: moisture (6.5-11.9%), crude fiber (12.0-28.8%), total carbohydrates (6.9-32.0%), protein (3.1-3.4%), and volatile oil (0.5- 5.1%) [24]. The volatile oil between these parts has the greatest trade value. The volatile components of cinnamon are classified in general to sesquiterpenes and phenylpropenes. The major component in cinnamon bark volatile oil is cinnamaldehyde shown in Figure (1), whereas, that the main component in cinnamon leaf oil is eugenol [25].

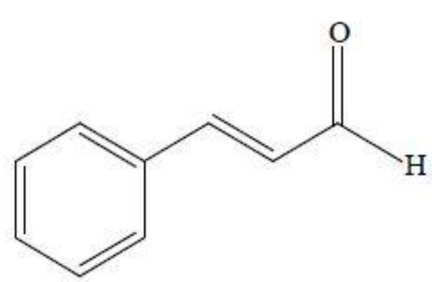

Figure 1. Cinnamaldehyde from Cinnamomum zeylanicum

Mechanisms of hypoglycemic activity of cinnamon

The mechanism of cinnamon in its antidiabetic activity and perhaps the effect of action at the pathway of insulin (Figure 2).

Cinnamtannin is a proanthocyanidin isolated from cinnamon which activates the phosphorylation of the insulin receptor β-subunit on adipocytes as well as other insulin receptors [26].

Cinnamon increases the quantity of glucose transporter 4 receptors as well as insulin receptors (IR) and insulin receptor substrates [27] thereby making it easier for glucose entry into cells. **Shen *et al.*** [28] explained that the extracts of Cinnamomum zeylanicum increase GLUT4 to the cell membrane of brown adipose tissue and muscle in a dose-contingent way. **Anand *et al.*** [29] showed a similar result of greater membrane translocation of GLUT4 in cinnamon treated rats than in controls.

Plaisier *et al.* [30] demonstrated cinnamaldehyde elevates the glucose transporter-1 (GLUT-1) mediated glucose absorption in a dose-dependent fashion in the L 929 fibroblasts. Meanwhile, in the presence of glucose shortage in the medium, cinnamaldehyde decreased the GLUT 1 mediated glucose absorption. **Hlebowicz et al in 2009** demonstrated a dose-dependent reduction of serum insulin concentrations and an increase in glucagon-like peptide 1(GLP-1) with cinnamon treatment. Improving glucose transport across cell membrane reducing insulin resistance [31].

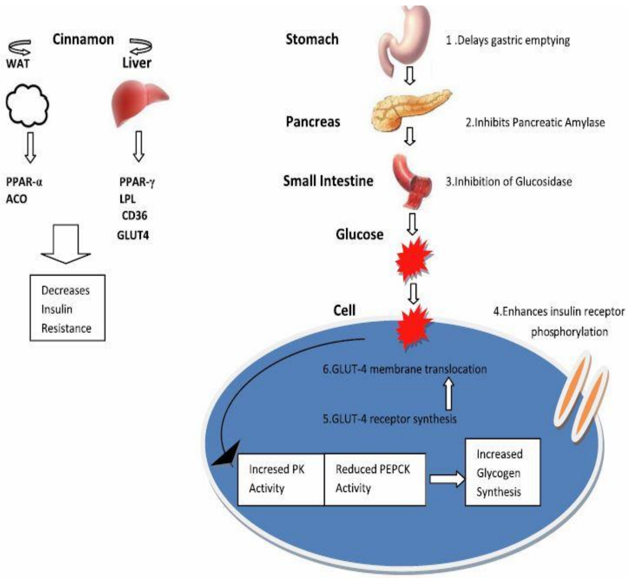

Figure 2. Mechanisms of cinnamon hypoglycemic activity.

Cinnamon influences

Strong proof indicates that cinnamon contains polyphenols compounds that appear to have insulin-like activity in rats, with type 2 diabetes. Moreover to find the molecular basis for the insulin-like activity of cinnamon, doubly linked procyanidin type-A polymers were used by **Cao *et al.*** [32] for illustrated cinnamon polyphenol compounds on the regulation of three of the proteins connected in the insulin signal transduction pathway, utilizing mouse 3T3-L1 adipocytes. Based on this investigation, it could be suggested that the cinnamon polyphenol compounds activate the insulin receptor (IR) by increasing their tyrosine phosphorylation activity and by reduced phosphatase activity [33].

Cinnamon polyphenol compounds increase the quantity of anti-inflammatory protein in the cells. These activities may lead to additional active glucose transport and use. Moreover, cinnamon polyphenols may supply one of the molecular bases for the useful influence of cinnamon, in making it better for people with diabetes by downregulating the synthesis of pro-inflammatory cytokines [33].

Bitter melon (*Momordica charantia*)

Bitter melon was used as food and medicine for a long time. Many plants are utilized as foods and medicines. These plants tend to be supportive, tonic and nourishing in nature These plants work effectively but seldom have strong hypoglycemic characteristics or powerful influences on affecting the reproduction tract and lowering blood sugar [34].

Momordica charantia or Bitter Melon belongs to family *Cucurbitaceae*. The bitter melon plant is used traditionally as both food and medicine. Bitter melon has been used for a long time as a hypoglycemic agent, where the plant extract has been regarded as vegetable insulin. A part of vegetable insulin bitter melon fruit is also used as tonic, stomachic, stimulant, emetic, antibilious, laxative and alterative. The fruit has various useful effects on the treatment of gout, rheumatism and even in curing diseases of spleen and liver [35].

Chemical constituents

Momordica charantia consists of the following chemical constituents those are alkaloids, momordicin and charantin (Figure 3)و also, more alkaloids [36]. *Momordica charantia* had contained glycosides, antinutritional factors, reducing sugars, resins, a natural antioxidant, essential oil, and free acids [37] and leaves are rich in minerals like calcium, magnesium, potassium, phosphorus, and iron; *Momordica charantia* and leaves are a large source of B vitamin complex [38].

The chemical constituents from Momordica charantia fruit as moisture, protein and lipids were 93.2, 18.02 and 0.76%, respectively, on a dry weight basis [39]. 45% of the seed is made up of oils (63–68% eleostearic acid and 22–27% stearic acid) [40]. Moreover, various glycosides were separated from the stem (*Momordica charantia*) [41] and *Momordica charantia* fruit [42] and are gathered in the genera of cucurbitane-type triterpenoids. Specifically, four triterpenoids have AMP-activated protein kinase activity which is a proposed hypoglycaemic mechanism of *Momordica charantia* [43].

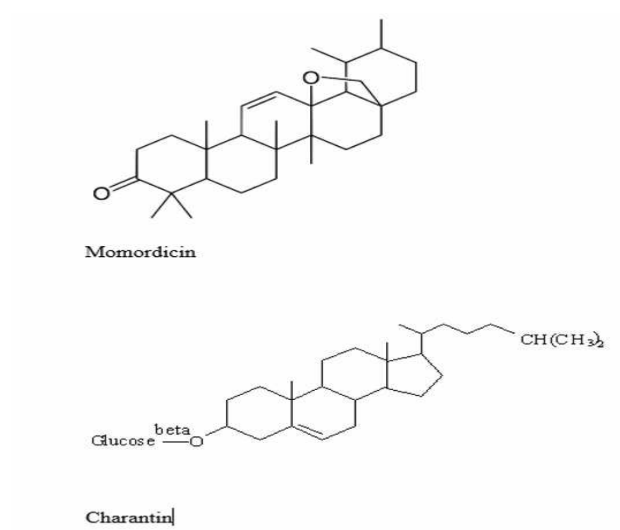

Figure 3: Chemical structure of momordicin and charantin

Regular use of bitter melon to control diabetes

Aswar and Kuchekar [44] proved that the anti-diabetic activity of Momardica charantia fruit extracts establishing the scientific basis for the utility of this plant in the treatment of diabetes. Bitter gourd contains bioactive compounds that activate a protein called AMPK (AMP-activated protein kinase α), which enables glucose uptake processes which lead to lowering glucose in the blood in patients with diabetes [45].

Bitter melon contains lectin, a bioactive compound that has an insulin-like activity which maybe because of its link together with 2 insulin receptors. Lectin lowers blood glucose concentrations through its action on peripheral tissues and, similar to insulins influence in the brain, reducing appetite. Also, the charantin is a powerful hypoglycemic agent of mixed steroids which are occasionally used in reducing the blood sugar levels [37, 46].

Gymnema Sylvestre (Gurmar)

Gymnema Sylvestre shows a wide range of therapeutic influences as an active natural therapy for diabetes, as well as hypercholesterolemia, cardiovascular diseases, infections, indigestion, and constipation. *Gymnema Sylvestre* has potential when it comes to treating diabetes as it shows good effects on blood sugar control, and stimulates regeneration of the pancreas. The *Gymnema Sylvestre* extract helps decrease body weight and improves lipid profile and for that reason is used in dietary supplements [47].

Mechanism action of Gymnemic acids

Mechanism action for the drug is through stimulation of insulin secretion from the pancreas Figure (4). As well it delays glucose absorption in the blood by attaching to receptors present in the external layer of the intestine, thereby preventing the absorption of sugar molecules by the intestine, leading to a reduction of sugar blood [48].

Hypoglycemic influence of gymnemic acids results from a cascade of events firstly from modulation of incretin activity which increases insulin excretion and release. Gymnemic acids decrease glucose and fatty acid assimilation in the small intestine and interfere in the ability of receptors in the mouth and intestine to the sensation of sweetness. [49]. Gymnemic acid has been shown to interact with GAPDH, a major enzyme in the glycolysis cycle [50]. Acyl moieties present in gymnemic acids play a significant role in GA-promoted smearing of GAPDH and G3PDH and play a significant role in the antihyperglycemic activity of GA derivatives [51].

Antidiabetic characteristics for Gymnema Sylvestre

A study to estimate the antioxidant activity of Gymnema leaf extract and the role of antioxidants in diabetic rats was carried out by **Kang *et al.*** [52] utilizing the ethanolic extract. Several antioxidant assays. Furthermore, liquid chromatography/mass spectrometry analysis revealed the presence of antihyperglycemic compounds like gymnemagenin and gymnemic acids in G. Sylvestre extract and the level of lipid peroxidation was reduced by 31.7% in serum, 9.9% in liver, and 9.1% in the kidney in diabetic rats fed with the ethanolic extract. [53].

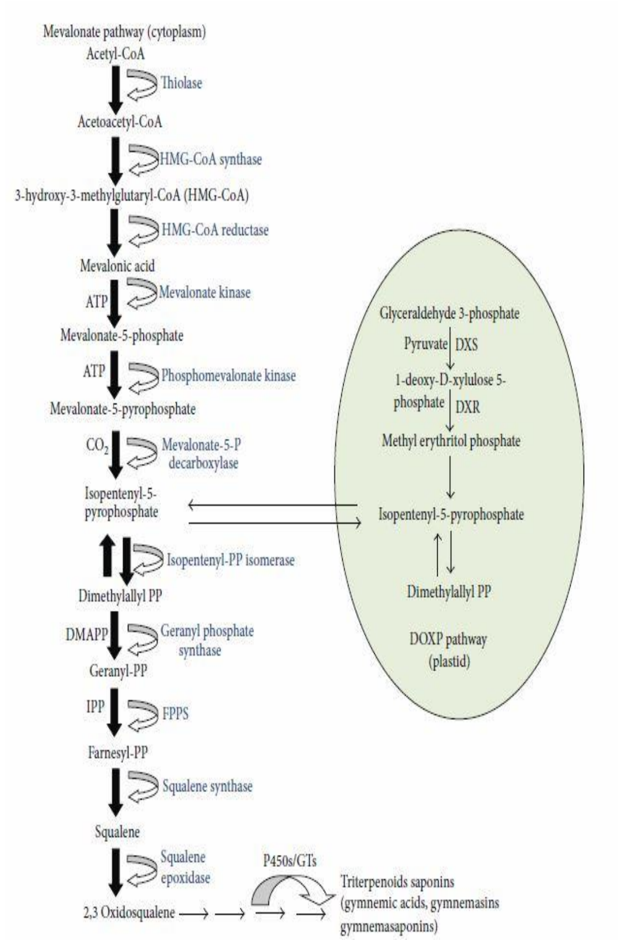

Figure 4: Hypothetical pathway of Gymnemic acid biosynthesis.

Ginger (*Zingiber officinale*)

It is presumed that oxidative stress plays a significant role in the secondary complications of diabetes. Finally, ginger could be lowering glycemic potential and reduce diabetic complications [54].

Bioactivity of ginger

Ginger contains many chemical constituents and could be presented as a powder [55]. The ginger chemical components could be volatile or non-volatile, the latter being responsible for the characteristic smell and taste of ginger. Among the volatile oil, compounds are sesquiterpene hydrocarbons like zingiberene, curcumin, and farnesene [56, 57]. Both gingerols and shogaols are very significant phenolic compounds since they have pharmacological characteristics that are useful to health as shown in Figure (5) [58].

Figure 5. An overview of the bioactivities of ginger

Mechanism of action of Ginger

Diabetes mellitus is recognized as a severe metabolic disorder that is caused by insulin shortage and/or insulin resistance, resulting in elevated blood glucose levels. Figure (6) summarizes the anti-hyperglycemic mechanisms and protective effect of ginger. The high glucose levels in the blood could accelerate protein glycation and the process of formation of advanced glycation end products (AGEs) [59, 60].

In one study, 6-gingerol was found to enhance glucose-encouraged insulin secretion and improve glucose tolerance in type 2 diabetic mice by elevating glucagon-like peptide 1 (GLP-1). 6-gingerol therapy activated glycogen synthase 1 and elevated cell membrane presentation of glucose transporter type 4 [61]. Furthermore, ginger extract therapy improves insulin sensitivity in rats with metabolic syndrome which might have been closely connected to the energy metabolism enhancement induced by 6-gingerol [62]. As well ginger extract reduces retinal microvascular alterations in rats that had diabetes induced by streptozotocin. The ginger growth factor in the retinal tissue [63].

Ginger has been found to modulate insulin release. In vitro, ginger extract augmented insulin release from the pancreatic β-cell in the rat. In arsenic-induced type 2 diabetic rats, [6]-gingerol showed a protective effect on pancreatic *β*-cells and restored the plasma insulin level [64]. The mechanism behind this action of ginger may involve interplay with the 5-HT3 receptor [65].

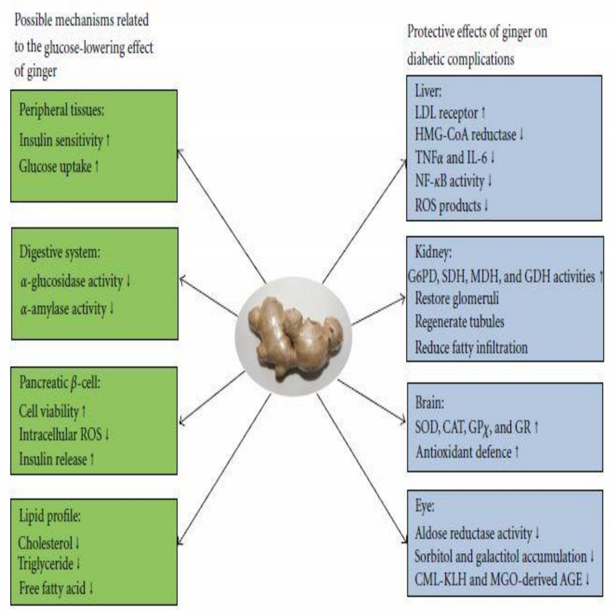

Figure 6: Summary of anti-hyperglycemic mechanism and protective effect of ginger

Olive leaf extract

Chemical constituents of olive leaf extract

Olive leaves (OLs) contain a large variety of phenols including rutin, flavones; flavan-3-ols, substituted phenols, oleoside and secoiridoid glycoside [66, 67].

Mechanism of antidiabetic action of olive leaf extract

de Bock *et al.* [68] reported that olive leaf extract (OLE) improves both insulin sensitivity and pancreatic β-cell secretory capacity after oral glucose challenge on overweight males. In another study, the treatment of diabetic rats with OLE significantly decreased HbA1c. However, **Wainstein *et al.*** in this study [69] did not measure the physical activities and diet type of the participants, so the independent effect of OLE alone could not be determined.

A recent study showed a correlation in the OLE treated group when α-glucosidase and α-amylase enzyme activities were compared with blood glucose levels [70]. It was found that the blood glucose levels were markedly attenuated while the enzyme activities decreased in the OLE group. OLE is considered to be effective in decreasing blood glucose levels by (i) inhibiting activity of carbohydrate digestive enzymes, α-glycosidase, and α-amylase, or (ii) downregulating gene expressions of these enzymes. Furthermore, this study demonstrated partial positive immunoreaction for insulin in β-cells through immunohistochemical analysis corroborating OLEs effect on insulin production seen in the de Bock et al study.

Antidiabetic medications such as acarbose, an a-glucosidase inhibitor, cause undesirable symptoms due to undigested starch in the colon [71]. Thus, tending toward alternative α-glucosidase inhibitors that are derived from natural sources and nutrients may be more effective, safe, tolerable and cheaper.

Berberine

Berberine is a traditional Chinese medicine extracted from Chinese rhizomacoptidis, cortex phellodendri, berberis, and other plants. In modern years there has been an increased number of studies in China to examine the treatment effects of Berberine in patients with diabetes**. Changrong *et al.*** [72] performed a randomized control trial of Berberine versus metformin and found Berberine effectively lowered blood glucose.

Antidiabetic effect of berberine

Berberine enhances glucose metabolism in type 2 diabetes mellitus by inhibition of liver gluconeogenesis through activation of AMPK (Adenosine Monophosphate Activated Protein Kinase) and also it ameliorates insulin sensitivity. Inhibition of liver gluconeogenesis leads to a reduction of fasting blood glucose levels. This is an insulin-independent action and includes mitochondrial inhibition by berberine [73].

Berberine activates AMPK leading to its increased phosphorylation resulting in consistent elevation of AMP/ATP ratio and reduction in the consumption of oxygen. Mitochondrial inhibition and an increase in AMP/ATP ratio result from AMPK activation by berberine [74]. Another mechanism explaining the antihyperglycemic action of berberine is its effect in increasing GLP 1 biosynthesis and its release [75, 76].

Moreover, berberine is recognized to modulate insulin secretion by pancreatic beta cells [77]. Metabolic syndrome occurs when AMPK regulated pathways are switched off and produce hyperglycemia, hyperlipidemia, hypertension, obesity, and inflammation. Only a few compounds can activate AMPK. Berberine is one of them and forms the basis for the treatment of metabolic syndrome [78]. Berberine also suppresses proinflammatory responses [79]. This action is mediated via AMPK activation as well.

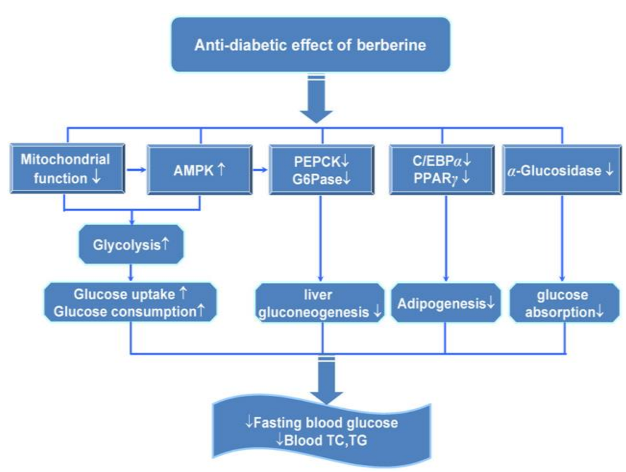

Figure 7. Anti-diabetic effect of berberine. Ming Zhang [80].

Conclusion

Diabetes mellitus is the most common endocrine disorder, Thus, therapy for diabetes mellitus using plant-derived compounds that are acceptable and do not need pharmaceutical synthesis to appear very attractive. All the herbal drugs mentioned in this review exhibit important clinical activity. Therefore, it would be recommended to carry out more research work on different plant species and their active compounds to provide evidence that certain traditional herbal therapies are beneficial in lowering blood glucose in patients with diabetes.

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