World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4239/wjd.v5.i2.176

World J Diabetes 2014 April 15; 5(2):176-197
ISSN 1948-9358 (online)

REVIEW

Phytotherapy in diabetes: Review on potential mechanistic perspectives

Hanan S El-Abhar, Mona F Schaalan

Hanan S El-Abhar, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Kasr El-Aini Str., 11562 Cairo, Egypt
Mona F Schaalan, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Misr International University, KM 28 Cairo, Egypt
Author contributions: El-Abhar HS and Schaalan MF solely contributed to this paper.
Correspondence to: Mona Schaalan, Associate Professor, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Misr International University, Cairo-Ismailia Road, KM 28 Cairo, Egypt. mona.schaalan@miuegypt.edu.eg
Telephone: +2-1-002011100 Fax: +2-1-02011100
Received: November 22, 2013 Revised: January 7, 2014
Accepted: March 13, 2014
Published online: April 15, 2014

Abstract

Diabetes mellitus (DM) is a widely spread epidemic disease that results from the absence of insulin, decreased secretion and/or impaired function. Since DM is a multifactorial disease, the available pharmaceuticals, despite their sensible treatment, target mostly one pathway to control hyperglycemia and encounter several side effects. Therefore, new therapeutic paradigms aim to hit several pathways using only one agent. Traditionally, antidiabetic plants and/or their active constituents may fulfill this need. More than 200 species of plants possess antidiabetic properties which were evaluated mostly by screening tests without digging far for the exact mode of action. Searching among the different literature resources and various database and in view of the above aspects, the present article provides a comprehensive review on the available antidiabetic plants that have been approved by pharmacological and clinical evaluations, and which their mechanism(s) of action is assured. These plants are categorized according to their proved mode of action and are classified into those that act by inhibiting glucose absorption from intestine, increasing insulin secretion from the pancreas, inhibiting glucose production from hepatocytes, or enhancing glucose uptake by adipose and muscle tissues. The current review also highlights those that mimic in their action the new peptide analogs, such as exenatide, liraglutide and dipeptidylpeptidase-4 inhibitors that increase glucagon-like peptide-1 serum concentration and slow down the gastric emptying.

Key words: Hypoglycaemic nutraceuticals; Antidiabetic phyto-constituents; Medicinal plants; Phytotherapy; Diabetes mellitus

Core tip: Diabetes is a serious metabolic disorder that is currently treated by different types of synthetic oral hypoglycemic agents, in addition to insulin. However, due to the unwanted side effects, the efficacies of these compounds are debatable and there is a demand for new compounds for the treatment of diabetes. Therefore, attention has been directed towards nutraceuticals originating from plants that are rich in antidiabetic phyto-constituents. Although the evidenced-based therapeutic usage of many plants is scarce, the plants cited in this review are those reputed traditionally for their antidiabetic effect and that were verified either experimentally or clinically.

El-Abhar HS, Schaalan MF. Phytotherapy in diabetes: Review on potential mechanistic perspectives. *World J Diabetes* 2014; 5(2): 176-197 Available from: URL: http://www.wjgnet.com/1948-9358/full/v5/i2/176.htm DOI: http://dx.doi.org/10.4239/wjd.v5.i2.176

INTRODUCTION

Diabetes mellitus (DM) is a common disorder of car-

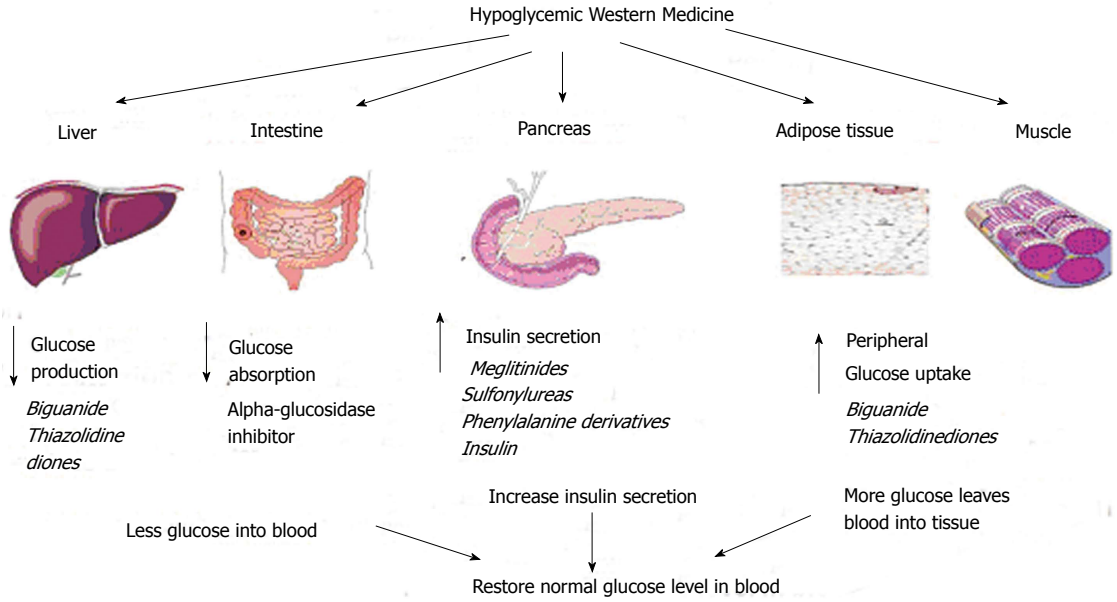

Figure 1 Pathophysiological mechanisms of hyperglycemia matched with the suitable pharmacotherapeutics (Data adapted from Hui *et al*[3]).

bohydrate, fat and protein metabolism reflected by an inappropriate fasting and postprandial high blood glucose levels (hyperglycaemia). This ailment results from the absence or scantiness of insulin secretion with or without concurrent impairment of insulin action. Consequently, the disease was classified into two types known as type I (insulin dependent, IDDM) and II (non-insulin dependent, NIDDM) according to the degree of the pancreatic defect. This classification has been even recognized since the time of Ibn Sinaa who mentioned it in his book "The Canon of Medicine".

DM is not confined to abnormal blood glucose level, but it progresses to affect other body systems. This fact was confirmed by several epidemiological studies and clinical trials that linked hyperglycemia to several complications at the macrovascular (coronary artery disease and cerebrovascular disease), as well as the microvascular levels (renal failure, blindness, limb amputation, neurological complications and pre-mature death)[1].

Based on the pathophysiology and severity of this disease, it can be controlled by dietary restriction, exercise, different types of synthetic oral hypoglycemic agents and/or insulin. Since DM is one of the multi-factorial based diseases, therefore, a balanced modulation of several targets can provide a superior therapeutic effect and a decrease in the side effects profile compared to the action of a single selective agent[2]. Hence, the current strategy used for the treatment of type II DM depends on combining an insulin secretagogue and an insulin sensitizer to provide a sensible therapeutic approach (Figure 1)[3]. Albeit reasonable management provided by these drugs, yet over time, some of the type II diabetic patients lose response towards conventional antidiabetics, leading to an inadequate control of their blood glucose level. Moreover, several side effects could hinder their capability in alleviating the symptoms of diabetes, such as severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness and even death. In addition, treatment of IDDM using insulin has also its complications, since continuous exposure to insulin causes a reduction in the number of receptors on the cell surface by promoting internalization, as well as degradation of hormone-occupied receptors[4].

In spite of the introduction and extensive utilization of hypoglycaemic agents, diabetes and its related complications continue to be a major health problem worldwide. Globally, around 150 millions of people are believed to be diabetic and the incidence rate is expected to double by 2025[5]. These expectations are "good to be true", especially for NIDDM, since the slothful lifestyle along with the high consumption of westernized diet, are considered to be the cornerstone for the development of this type of DM. Hence, it is a requisite to have safer and more effective oral hypoglycemic agents which can hit many targets to fulfill the new paradigm in drug discovery[6]. To achieve this objective, one may either employ a single compound to strike multiple targets; this can be termed as a one compound-multiple-target strategy[2], or use a combination of active compounds in one drug[7]. Therefore, attention has been directed towards nutraceuticals, since they can fulfill these criteria.

Herbal products may contain several active constituents or compounds that can act by several modes of action to influence multiple biological pathways and to alleviate the diabetic symptoms, providing thereby multifaceted benefits[8]. Nevertheless, this vision is not totally new, since prior to and after the discovery of insulin, herbs with hypoglycaemic effect have been used in folk medicine and are still prevalent[9-11]. As a support for this concept, metformin, which is notable for its substantial favorable impact on diabetes prevention, was purified from the French lilac *Galega officinalis* L.[12]. Moreover, the low cost of these compounds and the minimal side effects are

other reasons behind the hunt for effective natural agents to be used as complementary and/or alternative medicine.

Since restoring glucose homeostasis is influenced by several aspects, the current article classifies the hypoglycemic herbs that are available in literature resource from various database, into poroper categorization according to their potential mode of action to reduce blood glucose level. Different search engines were explored including Pubmed, Google, Asci database by using different keywords, as well as some of the traditional tertiary resources. Priority was given to research articles and information given by authentic organizations and federations. Plants cited in this review are those reputed traditionally for their antidiabetic effect and that were verified, either experimentally or clinically. The efficacy of hypoglycemic herbs is achieved by inhibiting glucose absorption from intestine, increasing insulin secretion from the pancreas, inhibiting glucose production from hepatocytes, or enhancing glucose uptake into the peripheral tissue *via* the glucose transporters (GLUT). Additionally, the plants that act by simulating the action of the new incretin peptide analogs were also mentioned in the present review.

INHIBITION OF GLUCOSE ABSORPTION

Postprandial hyperglycemia plays an important role in the incidence of type Ⅱ DM, since recent studies suggest that it could induce the non-enzymatic glycosylation of various proteins, resulting in the development of chronic complications. Therefore, controlling its level, *via* inhibiting the activities of α-glucosidase enzymes, is believed to be an important strategy to manage this disease. Alfa-glucosidase enzyme is a member of the glucosidases located in the brush-border surface membrane of the intestinal cells and is a rate-limiting step in the conversion of oligosaccharides and disaccharides into monosaccharides, necessary for gastrointestinal absorption[13]. In addition, α-amylase, which is present in both salivary and pancreatic secretions[14], is responsible for cleaving large malto-oligosaccharides to maltose which is a substrate for the intestinal α-glucosidase. Hence, the inhibition of α-glucosidase and/or α-amylase enzymes is currently in vogue, especially if these inhibitors stem from natural bases. The following are some examples of plants or their constituents that are proven to possess anti-enzymatic properties.

Methanolic extract of *Adhatoda vasica* Nees (*Acanthaceae*) was shown to have the highest sucrase inhibitory activity among forty species tested in an experimentally screening study by Gao *et al*[15]. This effect was attributed to its active constituents, *viz.,* vasicine and vasicinol, beside other constituents, offering thus, a possibility to develop successful α-glucosidase inhibitors. Previous studies by Gao *et al*[15] also reported the isolation of maltase inhibitory principles from the fruits of *Terminalia chebula*[16] and *Tussilago farfarae*[17].

Belonging to the same *Acanthaceae* family*, in vitro* studies on the ethanolic extract of *Andrographis paniculata* (*Burm. f.*) Nees and its principal active constituent, andrographolide (AG), seem to possess an antihyperglycemic activity[18]. They delay the quick digestion of starch, as well as sucrose, and prolong the absorption time of carbohydrates, pointing to an α-glucosidase inhibitory activity. Moreover, essential oils obtained from the woods of *Cedrus libani* A. Rich (*Pinaceae*), but not its leaves or cones, were able to inhibit the α-amylase activity[19].

Nigella sativa L. (*Ranunculaceae*), a plant commonly used in the Middle Eastern and North African traditional medicine was validated for its multi-factorial anti-diabetic actions. The crude aqueous extract tested in experimental rats was able to restore glucose homeostasis[20] and to improve glucose tolerance as efficiently as metformin. Apart from its effect to enhance insulin sensitivity in liver cells[21], and to possess an insulinotropic and insulin-like activities in cultured pancreatic β-cells, skeletal muscle cells and adipocytes[22], it is now documented[23] that the crude aqueous extract of *Nigella sativa* seeds directly inhibits the electrogenic intestinal absorption of glucose *in vitro*. This effect is mediated by reducing the intestinal sodium-dependent D-glucose cotransporter-1 (SGLT1) which is the major transporter of glucose in the intestine[24,25]. SGLT1 is also considered a key molecule in the sensing of glucose entry that is highly regulated by peptides and hormones[26].

Another plant that is widely used as an anti-diabetic in folk medicine in México is *Tournefortia hartwegiana,* where the decoction of its aerial parts controls the disease, when given orally for 10-14 d to alloxanized rats. The plant is thought to control the glucose level *via* several routes, including the inhibition of the intestinal α-glucosidase and other intestinal enzymes, as maltase and sucrase that are implicated in the digestion of polysaccharides and oligosaccharides[27,28]. The inhibitory effect of this decoction suppresses the absorption of carbohydrates from intestine and thereby reduces the post-prandial increase in the glucose level. On the other hand, Ortiz-Andrade *et al*[27] referred the anti-diabetic effect of the methanolic extract of the same plant to the enhancement of insulin secretion and/or action. Furthermore, other machineries , such as the modulation of the pancreatic and extrapancreatic effects[29-32], besides the enhancement of β-cell glucose metabolism or an activation of enzyme system generating cyclic adenosine mono phosphate (AMP) or phospholipid derived messenger[33], and/or blockage of glucose co-transporters from intestine to circulation[34], cannot be ruled out. These diverse mechanisms are attributed to the different components that were tested for their individual hypoglycemic action, where the "cocktail" of these constituents could trigger a synergic effect.

In 2004, Asano *et al*[34] in their search for an anti-glycosidase, succeeded to isolate new alkaloids from the bulbs of *Scilla peruviana* (*Hyacinthaceae*) that display an inhibitory action of bacterial β-glucosidase and bovine liver β-galactosidase to varying degrees. In addition, the methanolic extract of the rhizome of *Rheum emodi*, known as Himalayan rhubarb, inhibited the activity of both mild yeast and mammalian intestinal α-glucosidase as proven by Suresh Babu *et al*[35]. This action correlates with the

active components isolated from this rhizome such as chrysophanol-8-O-β-D-glucopyranoside, desoxyrhaponticin and torachrysone-8-O-β-D-glucopyranoside which showed a potent to moderate mammalian α-glucosidase inhibitory activity.

In a recent study, Loizzo *et al*[36] examined the influence of nine extracts of plant species collected in Lebanon, *viz*., Calamintha origanifolia, Satureja thymbra, Prangos asperula, Sideritis perfoliata, Asperula glomerata, Hyssopus officinalis, Erythraea centaurium, Marrubium radiatum and Salvia acetabulosa. The authors prepared different extractions with methanol, *n*-hexane and chloroform, yet the methanolic extracts of *Marrubium radiatum* and *Salvia acetabulosa* exerted the strongest activity against α-amylase and α-glucosidase. The leaf extract of the *Marrubium* related species, *viz., Marrubium vulgare*, is used in Brazilian and Mexican traditional medicine for its antidiabetic role, an effect that was documented clinically in patients with type Ⅱ non-controlled diabetes mellitus[37]. Several *Salvia* species have been reported for their hypoglycaemic effect in Iranian folk medicine[38,39] where they act by different mechanisms. For example, *Salvia lavandulaefolia* extract acts by decreasing the intestinal absorption of glucose, increasing the peripheral uptake of glucose, potentiating glucose-induced insulin release, and causing pancreatic islet cells hyperplasia[40].

The hypoglycemic mechanisms of another anti-diabetic plant, *Plantago ovata* husk, has also been studied and it was found that its aqueous extract hinders markedly the intestinal glucose absorption in rats; however, the extract failed to affect insulin secretion nor glucose transport in adipocytes[41].

Salacia species (*Celastraceae*) are widely distributed in East Asian countries and many plants from this genus (*e.g.*, *S. oblonga, S. reticulata* and *S. prinoides*) have been used for thousands of years in traditional medicines, particularly for the treatment of diabetes and obesity. Pharmacological studies have demonstrated that *Salacia* roots modulate multiple targets, including the inhibition of α-glucosidase, aldose reductase and pancreatic lipase, as well as the activation of peroxisome proliferator-activated receptor-alpha (PPAR-α)-mediated lipogenic gene transcription. All these mechanisms reinforce its usage in Ayurvedic medicine for diabetes and obesity. The methanolic extracts of *S. reticulata* and *S. oblonga* stems and roots reduced, dose-dependently, the postprandial hyperglycemia induced in rats by maltose, sucrose or starch, but not by glucose or lactose[42-44], pointing to their inhibitory effect on intestinal enzymes. Moreover, the aqueous extract of *S. reticulata* inhibited strongly the activities of α-glucosidase and α-amylase[42], while that of *S. chinensis* inhibited the α-glucosidase activity only[45]. These favorable effects are attributed to the identified components of the plant, *viz.,* mangiferin, salacinol, kotalanol and kotalagenin 16-acetate. Mangiferin causes concentration-dependent α-glucosidase inhibition *in vitro*[46], while salacinol, kotalanol and kotalagenin 16-acetate inhibited the increased serum glucose levels in maltose and sucrose loaded rats more than acarbose[43,44]. Thus, these findings suggest that the anti-diabetic property of *Salacia* is partially attributed to its intestinal α-glucosidase inhibitory activity.

Mangifera indica Linn. (*Anacardiaceae*) is a plant that possesses several properties, one of which is hypoglycemia that favors it to control type Ⅱ DM in some rural African communities[46]. Mangiferin is one of the active constituents of this plant, besides the polyphenolics, flavonoids, triterpenoids, and other chemical compounds. Therefore, the mangiferin-mediated inhibition of α-glucosidase activity[47], offers one mechanism for the hypoglycemic effect of this plant.

The potential antidiabetic activity of six pentacyclic triterpenes (oleanolic acid, arjunolic acid, asiatic acid, maslinic acid, corosolic acid and 23-hydroxyursolic acid) were isolated from the ethyl acetate extract of the leaves of *Lagerstroemia speciosa* (LSL) and were investigated by α-amylase and α-glucosidase inhibition assay[48]. However, the compounds showed week α-amylase inhibitory effect, while α-glucosidase was moderately inhibited, mainly by corosolic acid. In a search for an α-amylase inhibitory compound from plant origin, Ali *et al*[49] studied extracts of six selected Malaysian plants with a reputation of usefulness in treating diabetes using an *in vitro* model. Their work depicted that the hexane extract of *Phyllanthus amarus* had α-amylase inhibitory properties, an effect that was provoked by only three pure pentacyclic triterpenoids, namely, oleanolic acid, ursolic acid and lupeol.

The antidiabetic capacity of the standardized extract of maritime pine bark, derived from *Pinus pinaster*, Aiton. subs. Atlantica des Villar (Pycnogenol®), was documented clinically by Liu *et al*[50]. In their study a double-blind, placebo-controlled, randomized, multicenter study was performed with 77 type Ⅱ diabetic patients to investigate the potential antidiabetic effects of the French matitime pine bark extract, Pynogenol (100 mg) for 12 wk. Supplementation of Pycnogenol to conventional diabetes treatment loweres glucose levels and improves the endothelial functions, as evidenced by the significant reduction in HbA1c and endothelin-1. To characterize the possible mechanism of action, the authors attributed the effect of Pycnogenol to the suppression of α-glucosidase enzyme[50], rather than enhancing the insulin secretion, an effect that was more potent than green tea or acarbose[51]. The clinical antidiabetic effect was found also to be dose dependent and correlates positively with the procyanidins comprising of catechin and epicatechin subunits with varying chain lengths[52,53].

Another plant that is used extensively in folk medicine is the Fenugreek (*Trigonella foenum-graecum* L.), which is a member of the *Leguminosae* family, and is cultivated predominantly in Asia, the Mediterranean, and North African regions. Mainly the seeds are the part used for centuries for a wide range of diseases, as they were shown experimentally to possess significant hypoglycemic[54], antiathrosclerotic[55], anti-inflammatory[56], antinociceptive[57], antiulcerogenic[58], and antineoplastic effects[59]. Studies carried to elucidate its anti-diabetic mechanism(s) reveal that the plant works by inhibiting the intestinal glycosidase[60], in addition to its positive effect on glycolytic,

gluconeogenic, and lipogenic enzymes to restore glucose homeostasis in various animal models[60,61].

The *in vitro* α-glucosidase inhibitory model has been used by several research teams to verify the potential antidiabetic properties of different plant parts/extracts. In this context the antidiabetic effect of the Corni fructus (*Cornus officinalis Sieb. et* Zucc.) extract is mediated partly by inhibiting the α-glucosidase activity, an effect that reached to over 80% by one of the extract tested fractions[62]. Likewise, the alcohol extract of Alismatis Rhizoma-related hypoglycemic effect is mediated *via* the same mechanism, owing to its protostane-type triterpenes, besides promoting the glucose uptake *in vitro*[63]. Similarly, chemical components isolated from the safflower seed (*Carthamus tinctorius* L.)[64] and from the leaves of Ficus deltoidea, *viz.*, vitexin and isovitexin[65], as well as the methanolic extract of the aerial parts of Swertia corymbosa (used in Ayurveda herbal preparations in India)[66] exhibited *in vitro*/*in vivo* α-glucosidase inhibition.

Moreover, the same *in vitro* technique showed that the grape seed extract inhibits the intestinal α-glucosidases and α-pancreatic amylase that may delay carbohydrate digestion and absorption. Recently, this fact has been further documented, where grape seed extract has lowered the postprandial plasma glucose concentration in an acute, randomized, controlled crossover design study, in which healthy subjects received high carbohydrate meal with or without grape seed extract[67].

A prospective epidemiology links heavy coffee consumption to a substantial reduction in risk for type 2 diabetes, yet there is no evidence that coffee improves insulin sensitivity. Thus, it is reasonable to suspect that coffee influences the risk for beta cell "failure" that precipitates diabetes in subjects who are already insulin resistant. Indeed, coffee was proven to increase the production of the incretin hormone glucagon-like peptide-1 (GLP-1), possibly by its chlorogenic acid constituent (CGA-the chief polyphenol in coffee). The latter was also found to inhibit the intestinal glucose transport, as documented by the consumption of plants containing CGA, to be including coffee[68]. Further studies correlated the presence of CGA, the main polyphenolic compound in coffee, to the decreased diabetic risk where CGA slows carbohydrate absorption by its effect on the intestinal brush border membrane glucose transport, thus mimicking the effect of acarbose at the experimental level[69], as well as acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans[70]. CGA inhibits also the activity of glucose-6-phosphate translocase[71] which is now believed to play a role in glucose absorption[72,73]. In 2008, Andrade-Cetto *et al*[74] have tested the hypoglycemic effect of butanolic extracts of some Mexican plants and have found that *Malmea depressa* Baill R.E. and *Acosmium panamense* Benth. extracts resemble the effect of acarbose and decrease the plasma glucose level significantly by affecting the α-glucosidase enzyme. Nevertheless, the effect of the butanolic extract of *Cecropia obtusifolia* Bertol. was the most potent and it produced the highest reduction in the plasma glucose level that was even lower than the fasting level after 90 min, an effect that suggests an additive mechanism of action. This assumption could be true since this plant contains CGA which hits several targets in the diabetes metabolic pathways, besides its acarbose-like effect[75,76].

ENHANCEMENT OF GLUCOSE UPTAKE AND UPREGULATION OF GLUCOSE TRANSPORTERS

Stimulating the peripheral glucose uptake is one of the multiple mechanisms that control blood glucose level; hence, targeting this point is among the most promising goals for the treatment of type-Ⅱ DM. Basically, several factors assimilate to facilitate the glucose uptake process, including the activation of the GLUT in liver (GLUT-2), adipocytes and skeletal muscles (GLUT-4), the induction of the nuclear receptors, *viz.,* PPARs, especially the gamma subtype, as well as increasing the release of positive adipocytokines, such as adiponectin[77].

As illustrated in Figure 2, the cell membrane lipid bilayer is impermeable to carbohydrates, which necessitates the presence of specific transporters. These carriers are differentiated into two families, the first one is a sodium-linked GLUT that works actively and is limited to the intestine and kidney. The second family consists of eight homologous transmembrane proteins, GLUT-1-8, that are encoded by distinct genes, and they convey glucose by the facilitated diffusion down the glucose-concentration gradients[77]. However, the GLUT proteins have distinct substrate specificities, kinetic properties, and tissue distributions that dictate their functional roles. GLUT-1 is expressed in the brain, erythrocytes and endothelial cells, while GLUT-2 is found in the liver, kidney, small intestine, and pancreatic β-cells. This low-affinity GLUT (GLUT-2) has a role in sensing glucose concentrations in the islets of Langerhans. GLUT-3 is responsible for transporting glucose in neurons and placenta, while GLUT-4 is present in skeletal muscles, cardiac muscles and the adipose tissue. Of all the GLUT, only GLUT-4 is insulin-responsive. GLUT-5 has high affinity to transport fructose rather than glucose and it exists in the small intestine, sperm, kidney, brain, and adipose cells[77]. In 2003, Gorovits *et al*[78] found that GLUT-8, present in liver, plays a role in the regulation of glucose in case of diabetes. GLUT-4 is sequestered intracellularly and is translocated to the plasma membrane upon its stimulation by insulin. Thus, a decrease in the expression of GLUT-4 mRNA and protein reduced the insulin-mediated glucose uptake in diabetes[79]; in other words, imperfect GLUT-4 function could be a causative factor for insulin resistance[80].

From this point of view, herbs or their active constituents that can up-regulate GLUT-4 expression or that increase the translocation of this transporter could aid in the treatment of insulin resistance and hyperglycemia.

Cecropia obtusifolia Bertol (*Cecropiaceae*) is a plant extensively used for the empirical treatment of type Ⅱ diabe-

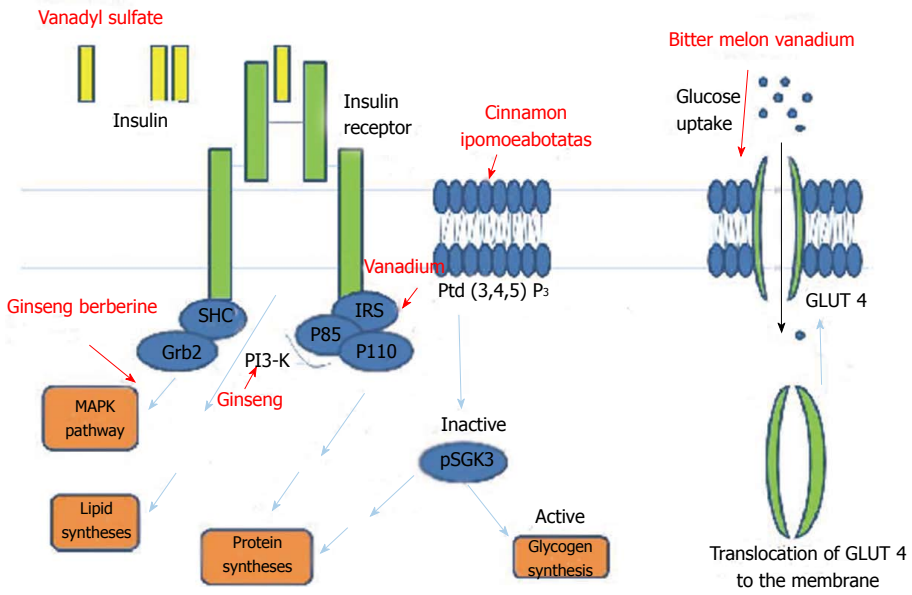

Figure 2 Insulin signaling pathway and insulin insensitive. The inner part of insulin receptor (IR) reveals a tyrosine kinase activity and coupled with multifunctional docking proteins IRS-1 and IRS-2. The in turn signaling leads to an activation of the MAPK cascade involved in mitogenesis and the open status of a hexose transporter protein (GLUTs) which is located in the cell membrane and is the only channel for glucose entery into cells. The decreased serine/threonine phosphorylation of IR, inactivates hexokinase and glycogen synthase, as well as defects in the phosphorylation of glucose transporter protein (GLUT4) and genetic primary defect in mitochondrial fatty acid oxidation, leading to insulin resistance and an increase of triglyceride synthesis contribute to this insulin insensitivity. The action sites of hypoglycemia herbs are indicated with red arrows[3].

tes in México[76]. The active hypoglycemic compounds found in this plant are CGA and isoorientin which are also found in other anti-diabetic plants as mentioned before[76]. In 2008, Alonso-Castro *et al*[76] studied the anti-diabetic mechanisms of *Cecropia obtusifolia* aqueous extract and its active compound CGA, and reported that the two preparations exert their anti-diabetic effects by stimulating glucose uptake in both insulin-sensitive and insulin-resistant adipocytes without appreciable pro-adipogenic effects. Thus, they could act by potentiating the insulin action or by activating a signaling pathway parallel to the insulin pathway.

Other anti-diabetic plants that act *via* increasing the glucose uptake in adipocytes, alone and in combination with insulin, include the ethanolic extract of *Amomum xanthioides* seeds[81], *Lagerstroemia speciosa*[82] and plants used by the Cree Nation in Canada, such as *Abies balsamea*, *Pinus banksiana* and *Rhododendron groenlandicum*[83]. Moreover, an aqueous extract from *Cinnamomum zeylanicum*[84], aqueous and ethanolic extracts of *Momordica charantia*[85], and aqueous extract of *Guazuma ulmifolia*[86], stimulated glucose uptake in 3T3-L1 adipocytes. However, none was evaluated on insulin-resistant adipocytes, except for *Guazuma ulmifolia*, which similar to *Cecropia obtusifolia,* mediated its action by stimulating glucose uptake in normal and diabetic adipocytes without inducing adipogenesis; nevertheless, its hypoglycemiant component(s) are not fully characterized.

Miura *et al*[87] validated the antidiabetic activity of *Lyophyllum decastes* (*Tricholomataceae*) in KK-Ay mice, an animal model of genetically type Ⅱ diabetes with hyperinsulinemia. The results of their work reported that mice receiving the aqueous extract showed an increase in the muscle content of GLUT-4 protein, which is responsible, at least in part, for decreasing insulin resistance. In 2004, Miura *et al*[88] again used the same model to test the hypoglycemic effect of corosolic acid, and found that it increased GLUT-4 translocation in muscle, without affecting the insulin level. This acid is one of the active constituents of *Lagerstroemia speciosa* L., banaba leaf. The plant is used traditionally in Philippines to treat diabetes and was studied by Takagi *et al*[89] who referred the antidiabetic effect to the inhibition of sucrose hydrolysis. However, the effect of corosolic acid on GLUT-4 can not be ruled out, although this requires further verification

In another study[90], the 3T3-L1 adipocytes were used to prove that the methanolic extract of *Liriope platyphylla Wang et Tang* (*LPWT*), *Liliaceae*, increased insulin-induced glucose uptake in adipocytes, by virtue of its homoisoflavone. This uptake was mediated through the translocation of GLUT-4 to the plasma membrane, *via* Insulin receptor Substrate - phosphatidyl inositol 3 kinase-Akt signaling mechanism. Aside from delaying the carbohydrate absorption *via* affecting α-glucosidase enzyme[19], *Andrographis paniculata* adopts another mechanism of action for its hypoglycemic effect through increasing the expression of GLUT-4. This was confirmed by the administration of its main constituent andrographolide in diabetic mice using streptozocin (STZ)[91].

Panax ginseng, also known as Korean red ginseng, appears to be a powerful anti-diabetic plant that has multi modes of action, due to its potent active constituents including ginsenoside Rh2. In a study by Lai *et al*[92], the authors reported that the ginsenoside Rh2 increases the gene expression of GLUT-4, at the mRNA and protein levels, in soleus muscle obtained from STZ-diabetic rats. They also suggest that the GLUT-4 expression is increased as a result of the increased β-endorphin secretion which will be detailed later in this review.

In an attempt to develop new substances for treating insulin resistance, obese Zucker rats were employed to screen the effect of myricetin, an active principle of *Abelmoschus moschatus* (*Malvaceae*), on insulin resistance[93]. The findings showed that myricetin increased insulin sensitivity by increasing the expression of GLUT-4 and by activating the phosphorylation of insulin receptor substrate-1. These results were also obtained from another study[94] using the methanolic extract of *Aegles marmelos*

and *Syzygium cumini* that are anti-diabetic medicinal plants used in Indian traditional medicine. The latter study reported an additive mechanism for lowering glucose level *via* the elevation of PPAR-γ, a nuclear receptor that will be discussed in the following section. *Azadirchata indica* Neem is among the Indian herbs that possess an antidiabetic effect. The hydroalcoholic extract of this herb exerted its antihyperglycemic activity by increasing glucose uptake, as well as glycogen deposition[95]. Furthermore, the anti-diabetic action of Tinospora cordifolia is mediated by increasing the expression of GLUT-4 by about 5 folds, as well as PPARα and γ, as tested in differentiated myocytes, L6 cells[96].

ACTIVATION OF THE NUCLEAR RECEPTOR PPAR-γ

The PPAR family belongs to type Ⅱ nuclear hormone receptors involved in the regulation of fatty acid, carbohydrate and glucose metabolism[97]. There are three isoforms of PPARs with specific tissue distribution and biological activity; they are identified as α, β or δ and γ with two subforms PPAR-γ1 and PPAR-γ2[98]. The receptors are ligand dependent, with the antidiabetic thiazolidinediones (TZDs) being the potent PPAR-γ agonist[97]. After their stimulation by their specific ligands, they regulate the transcriptional process *via* their heterodimerization with RXR, a retinoid X receptor, and then bind to peroxisome prolixferator-response element (PPRE)[97,98]. Clinical data demonstrated that the PPAR-γ agonists TZDs modulate glucose homeostasis by enhancing the peripheral glucose uptake through increasing GLUT-4 expression and translocation in adipocytes[99], as well as decreasing hepatic glucose output[100]. TZDs alleviate insulin sensitization by the redistribution of adipose deposits where these agents minimize visceral adipose content, responsible for the induction of insulin resistance, and redeposit it subcutaneously, in a phenomenon known as the "fatty acid steal" hypothesis[101]. In addition, activating PPAR-γ increased adipocyte fatty acid uptake, and decreased lipotoxic damage to insulin-sensitive tissues[102].

To date, the chief research interest in finding a nutraceutical compound(s) that mimics the PPAR-γ ligands constitute promising approaches for the treatment of diabetes, obesity and metabolic syndrome. Previously, multiple trials have shown conflicting results whether cinnamon lowers glucose or hemoglobin A1c (HbA1c). In 2009, Crawford[103] tested the cinnamon hypoglycemic activity in patients with type 2 diabetes through a randomized, controlled trial to evaluate whether daily cinnamon plus usual care versus usual care alone lowers HbA1c. Cinnamon lowered HbA1c (0.83%) compared with usual care alone lowering HbA1c (0.37%). Because one of the proposed mechanisms of cinnamon is increasing insulin sensitivity, hence, the treatment of patients with metabolic syndrome by adjunct cinnamon may yield weight loss, improved lipid profiles, and better glucose tolerance.

Park *et al*[104] used db/db mice, a typical non-insulin-dependent model, to study the anti-diabetic mechanism of Mulberry leaf water extract, Korean red ginseng and/or banaba leaf water extract. Herbs alone and their combination increased the expressions of liver PPAR-α mRNA and adipose tissue PPAR-γ mRNA in animals fed diets supplemented with the test herbs, in addition to restoring glucose and lipid homeostasis. Furthermore, the *Labiate* herbs rosemary and sage were documented in a recent study[105] as activators of the human PPAR-γ, possibly by their active constituents carnosol and carnosic acid.

What provides a potential validation for using traditional herbs as antidiabetics are the results of the screening study attained by Rau *et al*[106]. Among 52 ethanolic extracts, obtained from traditionally used herbs, the researchers found amazingly that nearly half the extracts activated PPAR-γ and 14 activated PPAR-α, while three of them were pan-PPAR activators, findings which were considered exceptionally high hit rate. The most active extracts were those of *Alisma plantago aquatica* (ze xie/European waterplantain), *Catharanthus roseus* (Madagascar periwinkle), *Acorus calamus* (sweet calamus), *Euphorbia balsamifera* (balsam spurge), *Jatropha curcas* (barbados nut), *Origanum majorana* (marjoram), *Zea mays* (corn silk), *Capsicum frutescens* (chilli) and *Urtica dioica* (stinging nettle).

The effect of the North American ginseng (*Panax quinquefolius*), a close relative to *Panax ginseng,* on glucose control was verified in a study by Banz *et al*[107], using male Zucker diabetic fatty rats. The findings showed that ginseng had marked effects on the expression of genes involved in PPAR actions and triglyceride metabolism. The authors encourage further research to determine the therapeutic value of this medicinal herb in treating human diabetes.

Green tea (*Camellia sinensis* L.) leaf extract on triglyceride and glucose homeostasis was evaluated in a fructose-fed insulin-resistant hamster model[108]. Supplementation of the green tea epigallocatechin gallate-enriched extract improves lipid and glucose homeostasis and increases the expression of PPAR-α and PPAR-γ proteins. These data suggest that intake of the green tea extract increases insulin-sensitivity, at least through boosting up PPAR.

Clematis species (*Ranunculaceae*) have been used continuously as anti-inflammatory agents by indigenous Australians. During examining the ethanol extract of *C. pickeringii*, *C. glycinoides* and *C. microphylla*, on COX-1, COX-2 and 5-lipoxygenase[109], the authors found that *Clematis pickeringii* has activated significantly the protein expression of both PPAR-α and PPAR-γ. These results merit the study of the potential antidiabetic mechanism(s) of these species. In a search for a natural PPAR-γ agonist, Atanasov *et al*[110] reported that the natural product honokiol from the traditional Chinese herbal drug Magnolia bark stimulates the basal glucose uptake in a comparable pattern to pioglitazone, but without inducing adipogenesis.

INCREASING ADIPONECTIN RELEASE

An additive role for PPAR-γ in the manipulation of glu-

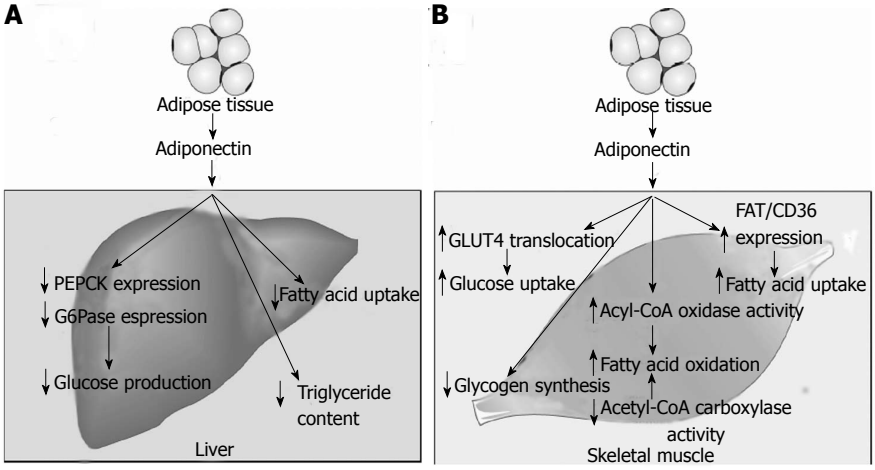

Figure 3 Effects of adiponectin on carbohydrate and lipid metabolism in liver and skeletal muscle (c.f. www.jpp.krakow.pl/.../articles/08_article.html[119]). FAT: Fatty acid translocase.

cose homeostasis is the modulation of adipocytokines. These bioactive substances are produced and secreted from adipose tissues which happened to be an endocrine organ[111]. Adipocytokines play central role in body insulin resistance, where the dysregulation of their production participates in the pathophysiology of the metabolic syndrome.

The plasma level of adiponectin is documented to be lower in patients with diabetes[112] and ischemic heart disease[113] than their age- and body mass index (BMI)-matched nondiabetic mates. This fact was further documented in a screening study on Japanese patients with type 2 diabetes and their age- and BMI-matched nondiabetic control subjects, and is attributed to the genetic mutation of the adiponectin gene associated with metabolic syndrome, including insulin resistant diabetes and atherosclerotic disease[114].

Consequently, adiponectin possesses antidiabetic and antiatherogenic properties[115]. The antidiabetic mechanism(s) involves enhancement of glucose uptake in skeletal muscles, activation of IRS-1-mediated phosphatidylinositol-3 kinase[115,116], acceleration of muscle β-oxidation *via* the activation of AMP-kinase[117], and suppression of hepatic glucose production[118,119]. These events are summarized in Figure 3.

Normal adiponectin plasma level is under the influence of PPAR-γ, where stimulation of this nuclear receptor potentiates its direct binding with the PPRE responsive element in the promoter region of the adiponectin gene, thus, enhancing the production and secretion of this cytokine.

Clinical studies now assure the beneficial effects of some plants in controlling glucose disorders. For instance, the extract of white-skinned sweet potato *Ipomoea batatas* (Caiapo) has been evaluated in type II diabetic patients, and was shown to control plasma glucose level through increasing insulin sensitivity along with the level of adiponectin[120]. Moreover, the mushroom *Agaricus blazei Murill* (ABM) extract was documented to improve insulin resistance and to elevate adiponectin level in subjects with type II diabetes receiving metformin and gliclazide; the latter cytokine provides at least one potential antidiabetic mechanism of this plant[121]. Concerning the antiatherogenic property of adiponectin, the extract of *Aronia melanocarpa* E. was administered to forty-four patients who survived myocardial infraction and have received statin therapy[121]. Compared to placebo, the chokeberry flavonoid extract increased adiponectin level, among other corrected parameters that nominate this extract as an adjunct therapy in patients with ischemic heart disease.

Momordica charantia owes its anti diabetic effect to its insulin-like action[122,123], antioxidant property[124,125], and glucose uptake enhancement[79]. The latter mechanism could be explained by the finding of Ryu *et al*[126], who stated that *Momordica*-induced glucose uptake is accompanied by, and may be the result of, increased adiponectin secretion, which is the communication between adipose tissue and skeletal muscle.

Adiponectin was also induced by the oral ingestion of *Plum ekisu*, tested on insulin- resistant obese Wistar fatty rats[127]. Dried plum is highly consumed in the West as a healthy food and is used in India as medicine to protect against geriatric related diseases, possibly by their phenolic compounds. Rats receiving plum concentrated juice showed better insulin sensitivity, increased PPAR-γ mRNA expression and marked elevation in adiponectin. These mechanisms are tightly correlated, where stimulation of PPAR-γ initiates the cycle, leading to increased production of adiponectin and alleviation of insulin sensitivity.

Apart from the multiple machineries by which *Salacia reticulate* extract mediates its antidiabetic effect[42], increasing the release of adiponectin adds also to these effects, which make it useful in the treatment of diabetes mellitus, insulin resistance and other metabolic diseases[128].

GLYCOGEM METABOLISM

Another cornerstone in controlling blood glucose level is the "hepatic output", which correlates with liver metabolic functions, including lipogenesis and glycogenesis. The latter process is precisely adjusted by adequate levels of insulin[129], which stimulates glycogen synthase and inhibits glycogen phosphorylase, resulting in the proper glycogen deposition in various tissues, especially skeletal

muscle. Since glycogen is the storable form of glucose, thus, insulin inadequacy initiates muscle protein breakdown to provide gluconeogenic precursors that could be the reason behind diabetes-induced weight loss. Consequently, compounds that enhance glycogen formation and/or increase its content in liver and muscles are considered beneficial anti-diabetic agents.

In an attempt to elucidate the anti-diabetic mechanism(s) of some plants used in the management of diabetes, it was found that *Caralluma sinaica* L. (*Asclepiadaceae*)[130] found in south Hejaz, west of Saudi Arabia, and Sinai region of Egypt, showed an anti-diabetic effect. This plant exerts its effect through opposing the STZ-induced glycogen depletion in liver and muscle, and by reversing weight loss in the diabetic rabbits, results that may be promoted by the realease of insulin.

Panax ginseng is suggested to induce glycemic control by sparing insulin and increasing glucose transport. Various preparations of *Panax ginseng* have been shown to upregulate insulin and non-insulin stimulated glucose transport in different animal models and cell lines[131-133]. Furthermore, *Momordica charantia* was able to renovate β-cells in the pancreas or partially destroyed ones[85] and to stimulate pancreatic insulin secretion[134]. These insulin-like properties[122,123] kindle glycogen storage by the liver and improve peripheral glucose uptake[126]. The anti-diabetic property of the aqueous extract of *Tamarindus indica* seed (*T. indica*) was also verified in a type I and II experimental models[135]. This action is mediated by restoring glycogen levels in liver and skeletal muscles, as well as inhibiting the glucose-6-P-ase activity. Increasing insulin level, however, was limited only to the type I model. Recently in 2012 the aqueous extract tested on STZ-induced diabetes showed that complex mechanisms stand behind its antidiabetic effect, such as β-cell neogenesis, calcium handling, as well as increasing GLUT-2 and GLUT-4. These findings show the scope for formulating a new herbal drug for diabetes therapy[136].

INSULINOMIMETIC AND INSULINOTROPIC EFFECT

In 2007, Eidi *et al*[137] studied again the hypoglycemic effect of the fenugreek seeds which was previously found to inhibit α-glucosidase, and they reported that the ethanolic extract significantly decreased serum glucose, triacylglycerol, cholesterol, urea, uric acid, AST, and ALT, whereas it increased serum insulin levels in treated STZ-induced diabetic rats. As a result, the authors concluded that fenugreek seeds extract encompasses antidiabetic activities similar to that observed for glibenclamide used as a standard drug. Eidi *et al*[138] have tested also the possible antidiabetic mechanism of Garlic (*Allium sativum*, *Liliaceae*) which is a common spice flavoring agent believed to lower plasma glucose level in diabetic patients. Therefore, using STZ-induced diabetic rats, they found that the alcoholic extract of garlic potentiates the insulin effect by increasing its pancreatic secretion from existing β-cells or its release from bound insulin. These effects are attributed mainly to the allicin-type compounds[139,140] which are disulphide compounds that can react with endogenous thiol containing molecules, such as cysteine, glutathione, and serum albumins to spare insulin from SH inactivation[141]. In another study, using STZ/high-fat diet Sprague Dawley rats, a comparison between the anti-diabetic effects of dietary freeze-dried ginger and garlic, was conducted. The experimental results revealed that ginger and garlic are insulinotropic rather than hypoglycemic, and that the anti-diabetic effects of ginger are better than those of garlic[142]. Using the same rat model, Islam *et al*[143] investigated the insulinotropic effect of dietary red chilli (*Capsicum frutescens* L.) in low and high concentrations and revealed that 2% dietary red chilli is insulinotropic rather than hypoglycemic at least in this experimental condition.

The effects of the ethanol extract and five partition fractions of the *Asparagus racemosus* root and *Ocimum sanctum* leaf were evaluated on insulin secretion together with exploration of their mechanisms of action. The ethanol extract and each of the hexane, chloroform and ethyl acetate partition fractions stimulated insulin secretion in isolated perfused rat pancreas, isolated rat islet cells and clonal β-cells. These findings reveal that constituents of both extracts have wide-ranging stimulatory effects on physiological insulinotropic pathways[144]. Similarly, the aqueous extract of *Asparagus adscendens* induced a significant increase in glucose-dependent insulinotropic actions in the clonal pancreatic β-cell line, enhanced glucose uptake in 3T3-L1 adipocytes and decreased starch digestion *in vitro*. These outcomes revealed that *Asparagus adscendens* possesses insulinotropic, insulin-enhancing activity and inhibitory effects on starch digestion[145].

The antihyperglycemic action of *Stevia rebaudiana (Asteraceae)* Bertoni leaves extracts were confirmed using type II diabetic Goto-Kakizaki rats[146]. The large quantities of the glycoside stevioside in the *Stevia rebaudiana* leaves are responsible for the anti-hyperglycaemic, insulinotropic, and glucagonostatic actions of the herb; results which support the traditional use of this herb in the treatment of diabetes in Paraguay and Brazil. Similar efficacy pattern was obtained by the crude extract of *Viscum album* (*V. album*) leaf which produced about 35.3% decrease in glucose concentration in STZ-induced diabetic rats and stimulated insulin secretion by about 81.5%. Although, only a subtle suppression in glucagon level was observed, yet it was significant. Thus, the *V. album* leaves extract may possess antihyperglycaemic, insulinotropic, and possibly, mild glucagonostatic agent(s) and may, therefore be a candidate for the anti-diabetic drugs[147].

Butanol extract of *Zizyphus spina-christi* L. (*Rhamnaceae*) leaves and its major saponin glycoside, christinin-A, were tested to evaluate their effect on serum glucose and insulin levels in non-diabetic control, type- I and type- II diabetic rats[148]. Both the extract and the saponin compound improved the oral glucose tolerance , potentiated glucose-induced insulin release, reduced the serum glucose level and increased the serum insulin level of non-diabetic control

and type-Ⅱ diabetic rats, but not those of type-Ⅰ diabetic rats. They also enhanced the glucose lowering and insulinotropic effects of glibenclamide. The data pointed to the insulinotropic capacity of the tested plant.

Furthermore, in traditional Nepalese folk medicine the leaf extract of the annual herb *Biophytum sensitivum* is used for the treatment of hyperglycemic patients. This property was documented by Puri[149] who ascribed the leaf extract hypoglycemic response to its insulinotropic effect, where he found that the tested extract induces the release and/or synthesis of insulin.

Similar insulinotropic effect was presented by pterostilbene, a flavonoid constituent derived from the wood of *Pterocarpus marsupium,* a herb used in the Indian folk medicine; the active compound causes pancreatic β-cell regranulation[150]. Marsupin, pterosupin and liquiritigenin obtained from the plant showed also antihyperlipidemic activity. Moreover, epicatechin, an active principle, has been found to be insulinogenic, enhancing the insulin release and the conversion of proinsulin to insulin *in vitro.* Like insulin, epicatechin stimulates oxygen uptake in fat cells and increases glycogen content of rat diaphragm. Aloe vera (Liliaceae) exerts its hypoglycemic effect in rats by its bitter principle through stimulating the release of insulin from the β-cells of Langerhans as documented after the use of single, as well as repeated doses of the bitter principle of the Aloe vera in diabetic rats[150]. Other insulinptropic Indian herbs include *Acacia Arabica* (Babhul), *Eugenia jambolana* (Indian gooseberry), *Annona squamosa* (sugar apple), *Caesalpinia bonducella* (Fevernut), *Hibiscus rosa-sinesis* (Gudhal), *Scoparia dulcis* (sweet broomweed) and *Tinospora crispa*[96].

Patel *et al*[151] presented a thorough review on 65 species of plants with insulinomimetic or insulin secretagogue. Most of these belong to the family Leguminoseae, Lamiaceae, Liliaceae, Curcubitaceae, Asteraceae, Moraceae, Rosaceae and Araliaceae. The most active plants are Allium sativum, Gymnema sylvestre, Citrullus colocynthis, Trigonella foenum greacum, Momordica charantia and Ficus bengalensis. *Citrullus colocynthis* (Cucurbitaceae) pulp ethanolic extract at 300 mg/kg, *p.o.* was found to increase insulin and decrease plasma glucose levels significantly in alloxan-induced diabetic rats. Moreover, the aqueous extract also showed a dose-dependent increase in the insulin release from isolated islets, as well as other different extracts, such as crude extract, aqueous, alcoholic, purified extract and beta-pyrazol-1-ylalanine, the major free amino acid derivative present in the seeds[151].

Trigonella foenum-graecum has been observed to cause glucose-induced insulin release *in vitro* and *in vivo*. 4-Hydroxyleucine, a novel amino acid from fenugreek seeds, increased glucose-stimulated insulin release from isolated islet cells in rats, mice and humans, and possibly hydroxyisoleucine which represents 80% of the free amino acids in *Trigonella foenum-graecum* seeds. The extracts, powder and gum of *Trigonella foenum-graecum* seeds may help to improve insulin sensitivity presumably due to the presence of fibers, which slow the metabolism of carbohydrates, resulting in reduced insulin levels and lowered blood glucose[151].

Alcoholic extract of *Gymnema sylvestre* (Asclepiadaceae) stimulated insulin secretion from the rat islets of Langerhans and several pancreatic β-cell lines. In another study, the oral administration of the water-soluble leaves extract (400 mg/d) to 27 IDDM patients on insulin therapy lowered their fasting blood glucose and their insulin requirements. In type II diabetic patients on *Gymnema sylvestre* supplementation the pancreatic β-cells is suggested to be regenerated or repaired as supported by the raised insulin levels in their serum. This assumption has been concluded also when the number of the pancreatic islet and β-cells, as well as insulin levels wre increase after oral administration of the aqueous extract to diabetic rats. Gymnemic acid molecules dihydroxy gymnemic triacetate had the ability to release the insulin by the stimulation of a regeneration process and revitalization of the remaining β-cells. The aqueous extract of *Gymnema sylvestre* leaves stimulated insulin secretion from mouse cells and isolated human islets *in vitro*, without compromising cell viability[151].

Among the glucagonostatic Indian herbs are *Caesalpinia bonducell, Coccinia indica, Boerhavia diffusa, Enicostema littorale and Murraya koenigii.* These herbal extracts increase glycogenesis, restore the activities of lipoprotein lipases and decrease the glucose-6-phosphatases, thereby inhibiting the glycogenolysis, and gluconeogenesis processes, as well as increasing the peripheral glucose utilization[150].

In a recent study, the ethanolic extract of ethanolic extract of Schizandra arisanensis and its isolated constituents provided some insulinotropic effects by ameliorating cytokine-mediated β-cell death and dysfunction *via* anti-apoptotic and insulinotropic actions[152].

ELEVATION OF D-CHIRO-INOSITOL

D-chiro-inositol (D-CI) is a rare inositol isomer present in inositol phosphoglycans (IPGs) which are putative insulin second messengers. These mediators are released from cell membranes, cells and human blood by insulin and other growth factors[153] and mediate some, but not all, of insulin actions[154]. D-CI acts as an insulin surrogate where it exhibited an anti-hyperglycaemic effect *in vivo*[155], and enhanced insulin-induced glucose incorporation into glycogen, *in vitro*[155]. Albeit, D-CI modulates favorably insulin's effect on peripheral glucose utilization under physiological conditions, Kennington *et al*[156], reported abnormal low or immeasurable levels of D-chiro-inositol in urine and muscle from type Ⅱ diabetic patients, suggesting that D-CI deficiency might be related to the insulin resistance. Accordingly, D-chiro-inositol when administered to STZ diabetic rats[157] and humans[158] decreased hyperglycemia and enhanced glucose disposal (Table 1).

Cucurbita ficifolia is traditionally used in Asia for the management of diabetes; however, its mechanism of action was not clarified. In 2006, Xia *et al*[159] found that *C. ficifolia* may be a natural source of D-CI which is present in fairly high levels in this plant and may be the cause for its anti-diabetic character. Using STZ diabetic rats,

Table 1 Following is a list of plants that are reported to have insulin mimetic or insulin secreatory action

1 Abies pindrow (Pinaceae)	34 Momordica charantia (Cucurbitaceae)
2 Aegle marmelos (Rutaceae)	35 Mucuna pruriens (Leguminosae)
3 Agrimony eupatoria (Rosaceae)	36 Nigella sativa oil (Ranunculaceae)
4 Aloe barbadensis (Liliacea)	37 Olea europia (Oleacea)
5 Annona squamosa (Annonacea)	38 Panax ginseng (Araliaceae)
6 Averrhoa bilimbi(Oxalidacea)	39 Pandanus odorus (Pandanaceae)
7 Bixa orellana (Bixaceae)	40 Parinari excelsa (Chrysobalanaceae)
8 Boerhaavia diffusa (Nyctaginaceae)	41 Prunella vulgaris (Labiatae)
9 Bougainvillea spectabilis (Nyctaginaceae)	42 Psidium guajava (Myrtaceae)
10 Brassica nigra (Cruciferae)	43 Pterocarpus marsupium (Fabaceae)
11 Camellia sinensis (Theaceae)	44 Radix glycyrrhizae (Fabaceae)
12 Capsicum frutescens (Solanacea)	45 Radix rehmanniae (Scrophulariaceae)
13 Catharanthus roseus (Apocyaceae)	46 Rehmania glutinosa (Scrophulariacea)
14 Cinnamon zeylaniucm (Lauraceae)	47 Ricinus communis (Euphorbiaceae)
15 Coccinia indica (Cucurbitaceae)	48 Salvia lavandifolia (Lamiacea)
16 Cornus officinalis (Cornaceae)	49 Sarcopoterium spinosum (Rosaceae)
17 Elephantopus scaber (Asteraceae)	50 Scoparia dulcis (Scrophulariaceae)
18 Enicostemma littorale (Gentianaceae)	51 Selaginella tamariscina (Selaginellaceae)
19 Ephedra distachya (Ephedraceae)	52 Semen coicis (Ggramineae)
20 Eriobotrya japonica (Rosaceae)	53 Smallanthus sonchifolius (Asteraceae)
21 Euccalyptus globulus (Myrtaceae)	54 Stevia rebaudiana (Asteraceae)
22 Fermented unsalted soybeans	55 Swertia chirayita (Gentianaceae)
23 Ficus bengalensis (Moraceae)	56 Swertia punicea (Gentianaceae)
24 Genistein	57 Syzygium cumini (Rutaceae)
25 Ginkgo biloba (Ginkgoaceae)	58 Tabernanthe iboga (Apocynaceae)
26 Helicteres isora (Sterculiaceae)	59 Teucrium polium (Lamiaceae)
27 Hibiscus rosa (Malvacea)	60 Tinospora crispa (Menispermaceae)
28 Hordeum vulgare (Gramineae)	61 Tribuluks terrestris (Zygophyllaceae)
29 Ipomoea batata (Convolvulaceae)	62 Urtifca dioica (Urticaceae)
30 Juniperus communis (Pinacea)	63 Vinca rosea (Apocyanacea)
31 Lausena anisata (Rutacea)	64 Zingiber officinale (Zingiberaceae)
32 Lepechinia caulescens (Lamiaceae)	65 Zizyphus spina-christi (Rhamnaceae)
33 Medicago sativa (Fabaceae)	

the fruit extract of *C. ficifolia* lowered the blood glucose level and increased the hepatic glycogen content, and the plasma insulin. Furthermore, the same extract improved the blood glucose tolerance when an oral glucose tolerance test was performed in fasted diabetic and normal rats. The results of this experimental animal study lend a pharmacological credence to the suggested folkloric uses of the plant in the management and control of diabetes mellitus, owing to its high content of the insulin-mimetic, D-CI. This compound is also the active constituent of *Fagopyrum tataricum* L. Gaench that possesses an insulin-like bioactivity. Yao *et al*[160] illustrated that the D-CI-enriched extract of *Fagopyrum tataricum* lowered plasma glucose, C-peptide, improved glucose tolerance, and enhanced insulin immunoreactivity in KK-Ay mice.

INCRETIN MIMETICS AND INCRETIN ENHANCERS

A new target for the management of type Ⅱ DM is the gut hormone, GLP-1 (incretin) which is secreted as a riposte to meal. This hormone maintains glucose balance by different routes where it stimulated glucose-dependent insulin secretion, delays gastric emptying, inhibits glucagon secretion, and protects or even exerts a trophic effect on β-cells, as illustrated in Figure 4. However, the hormone is rapidly degraded by dipeptidylpeptidase-4 (DPP-4), an enzyme that inactivates also glucose-dependent insulinotropic peptide (GIP)[161]. Thus, the aim in pharmaceutical research is either to inhibit DPP-4, to prolong GLP-1 duration of action, or to use compounds that can partially resist DPP-4. These compounds are either incretin-mimetic agents that simulate GLP-1 (exenatide) or a long-acting incretin analogue (liraglutide)[162]. Incretin, thus, challenged the pharmaceutical researchers to find a nutraceutical compound that could modulate this hormone.

In this regard, recent data reported that inulin-type fructans extracted from chicory roots regulated glucose and lipid homeostasis by enhancing colon production of GLP-1. Therefore, Urías-Silvas *et al*[163] evaluated the fructans extracted from *Agave tequilana* Gto. and *Dasylirion spp.* on glucose and lipid metabolism. The data showed a decrease in body weight of mice fed fructans-containing diet, besides the restoration of glucose and lipid levels. As a conclusion, the authors reported that fructans from any botanical origin initiates the production of GLP-1 from colon, and it is responsible for the amendment of glucose and lipid metabolism.

The potential antihyperglycemic activity of an ethanolic extract of *Artemisia dracunculus* L., called Tarralin, in diabetic mice was studied by Ribnicky *et al*[164]. This extract posed a positive antidiabetic action, *via* decreasing the mRNA expression of phospho-enolpyruvate carboxykinase (PEPCK), the main catalyzing enzyme in gluconeogenesis, and increasing the binding of incretin (GLP-1) to its receptor.

Impairment of β-cell function results from the improper insulin/IGF-1 signaling cascade through insulin receptor substrate-2 (IRS-2). Thus, induction of IRS-2 in β-cells can potentiate its function and mass, an effect that was attained by the GLP-1 receptor agonist, exendin-4, through elevation of intracellular cyclic Adenosine mono phosphate (cAMP)[165]. GLP-1/exendin-4 is known to enhance glucose-stimulated insulin secretion and to increase β-cell transcription factors, such as pancreas duodenum homeobox-1 (PDX-1), to promote β-cell growth and survival[165]. These promising actions of exendin-4 were associated with the induction of IRS-2, the pathways of

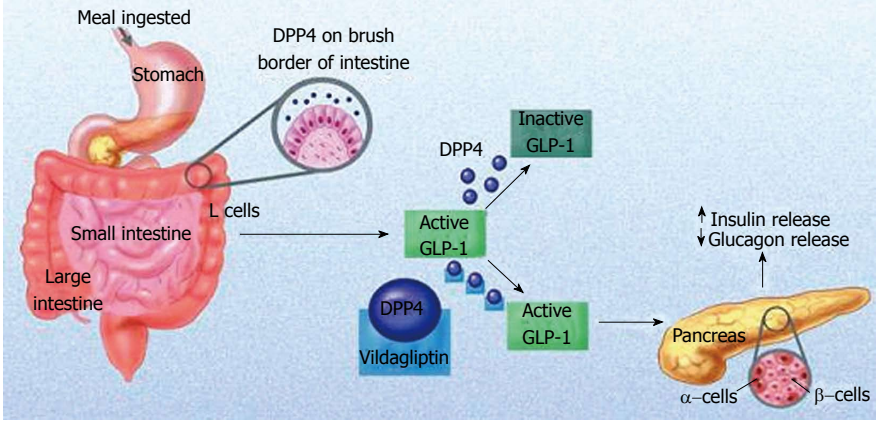

Figure 4 Effects of active glucagon-like peptide-1 and dipeptidylpeptidase-4 on glucose homeostasis [(c.f. www.medscape.com) Am J Health Syst Pharm, 2007]. GLP-1: Glucagon-like peptide-1; DPP-4: Dipeptidylpeptidase-4.

which play an important role in β-cell expansion, and augmentation of insulin secretion.

In a recent study, Park *et al*[165] examined the potential antidiabetic mechanism(s) of six herbs used in Chinese medicine to treat diabetes. These herbs were *Galla rhois*, *Rehmanniae* radix (*Rehmannia glutinosa* Liboschitz var. *purpurea* Making), *Machilus* bark (*Machilus thynbergii* Siebold et Zuccarini), *Polygonatum* radix (*Polygonatum odoratum* Miller Druce), *Ginseng* radix (*Panax ginseng* C.A. Meyer), and *Scutellariae* radix (*Scutellariae baicalensis* Georgi). The authors reported that these herbs induced IRS-2 in rat islets, improved glucose-stimulating insulin secretion and increased β-cell survival. In addition, *Rehmanniae* radix, *Ginseng* radix and *Scutellariae* radix were found to mediate insulin secretion through cAMP/PKA-dependent and/or -independent pathways. These herbs also induced PDX-1 and glucokinase, besides the increased expression of IRS-2. Activation of glucokinase could vindicate the enhancement of glucose stimulated insulin secretion, while induction of PDX-1 was associated with β-cell proliferation[165]. The promising effects of *Ginseng* radix and *Scutellariae* radix could be ascribed to the active constituents, ginsenosides and the flavonoid baicalein, respectively. The finding, hence, point to the presence of natural agents that possess incretin-like action and that mimic exendin-4.

ROLES OF ENDOGENOUS OPIOIDS ON GLUCOSE HOMEOSTASIS

Apart from the well known pharmacological actions of opiates, their binding to opioid receptors located in the pancreatic β-cells and their ability to manipulate diabetic disorders has been documented[166]. The opioid peptide β-endorphin, secreted from the adrenal gland[167] has been shown to induce insulin secretion also *via* activating the pancreatic opioid receptors[168]. Besides, this peptide also was found to regulate glucagon and somatostatin release from isolated islets of Langerhans[169,170]. Therefore, increased glucose utilization and decreased hepatic output may be a consequence to the increased release of β-endorphin and the activation of peripheral opioid μ-receptors (MOR). Activation of these receptors might enhance the expression of muscle GLUT and/or reduce hepatic gluconeogenesis at the gene level[171]. MOR-induced glucose uptake is accomplished by increased gene expression of GLUT-4 *via* a phospholipase C-protein kinase (PLC-PKC) dependent pathway[172]. It has also been observed that stimulation of α_1-adrenoceptors in the adrenal gland provokes the secretion of β-endorphin[173] depending also on the PLC-PKC pathway[174,175].

In STZ-diabetic rats, Hsu *et al*[176] stated that β-endorphin biosynthesis increases in the adrenal gland, along with the opioid μ-receptors gene expression[177]; events that may compensate for the glucose disturbed homeostasis. Therefore, development of pharmaceutical or nutraceutical agents that target β-endorphin secretion and/or stimulate peripheral MOR, *via* an insulin-independent action, donates a new hit that may have merit in glycemic control.

Since application of herbal plants or their products in the management of glucose metabolism is extensively searched, investigations were conducted to study their potential effect on β-endorphin and peripheral opioid μ-receptor. One of the early studies in this regard, is that carried out by Hsu *et al*[178] using caffeic acid, which is a phenolic compound contained in the fruit of *Xanthium strumarium*. After an intravenous injection of caffeic acid into diabetic rats of both STZ-induced and insulin-resistant models, a dose-dependent decrease in the plasma glucose was observed; moreover, it increased the glucose uptake in isolated adipocytes. This trial was followed by another study[179] to verify the mechanism of caffeic acid using STZ-induced diabetic rat. In this experiment, caffeic acid increased the release of β-endorphin from the adrenal gland through the activation of α_{1A} -adrenoceptors. These receptors were adopted as one of the antidiabetic mechanisms of andrographolide present in the leaves of *Andrographis paniculata* (*Burm. f.*) Nees. Using cultured myoblast C2C12 cells, andrographide was documented to activate these adrenoceptors *via* PLC-PKC dependent pathway to fascilitate glucose uptake[180]. Inhibiting α-glucosidase[19] and increasing GLUT-4 mRNA[91] were other mechanisms mediated by this active constituent. A recent study by Yu *et al*[181] validated the andrographolide-induced α_{1A}-adrenoceptors activation in type I diabetes-like animals, which enhance β-endorphin release that in turn stimulates the opioid micro-receptors. The authors reported also an increased expression of the GLUT-4 in

soleus muscle and a reduced expression of PEPCK in liver, effects that may explain the registered reduction in hepatic gluconeogenesis and enhancement of the glucose uptake. A similar pattern was recorded to rationalize the antidiabetic mechanisms of myricetin, the active principle of *Abelmoschus moschatus* (*Malvaceae*) using STZ-diabetic rats[182]. Myricetin, in insulin-deficient animals, activated peripheral MOR, in response to increased β-endorphin secretion. Opioid μ-receptor activation is held responsible for the enhancement of muscle *GLUT-4* gene expression and the attenuation of hepatic *PEPCK* gene expression observed in these myricetin-treated diabetic animals.

Another study was carried out to investigate the antihyperglycemic mechanisms of syringin, an active principle purified from the rhizome and root parts of *Eleutherococcus senticosus* (*Araliaceae*). STZ-diabetic rats showed an increased release of β-endorphin from the adrenal medulla after receiving a bolus intravenous injection of syringing[183]. Niu *et al*[183] concluded that the decreased plasma glucose, in the diabetic rats lacking insulin, is mediated by the effect of β-endorphin on peripheral micro-opioid receptors.

The antidiabetic potency of isoferulic acid, one of the active components in *Cimicifugae rhizoma*, is attained by lowering glucose level, improving glucose uptake in skeletal muscle along with inhibiting hepatic gluconeogenesis in rats with an insulin deficiency[184]. For precise clarification of its mode of action, Liu *et al*[185] tested its impact on the α_{1A}-adrenoceptor/β-endorphin system in a STZ diabetic rats. Formerly, Liu *et al*[186] showed that isoferulic acid can activate α_{1A}-adrenoceptor, leading to increased glucose uptake into cultured mouse myoblast C2C12 cells; however, the role of β-endorphin in the plasma glucose-lowering action of isoferulic acid is still unclear. In this work[187], the authors proved that isoferulic acid increased β-endorphin level *via* affecting α_{1A}-adrenoceptors, leading to stimulation of peripheral opioid receptors, resulting in increased expression of GLUT-4, and reduction of hepatic gluconeogenesis. Moreover, the same laboratory examined the mechanism(s) of plasma glucose lowering action of puerarin in STZ-induced diabetic rats and concluded that this isoflavone can act as a ligand to activate α_{1A}-adrenoceptors on the adrenal gland to initiate the aforementioned cascades[187].

ANTIOXIDANTS

In the course of normal aerobic metabolism, oxygen free radicals are produced during the reduction of oxygen into water. Since these radicals are inherently toxic, cells have built up defense systems to quench them. These defense systems are either enzymatic, including superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione reductase and glucose-6-phosphate dehydrogenase, or non-enzymatic, such as vitamins C and E as well as thiols, especially the reduced glutathione molecule[188]. If these oxygen free radicals, referred as reactive oxygen species (ROS), are excessively produced and are able to overwhelm the endogenous defense systems, then a state of oxidative stress originates. These ROS can bind with most normal cellular components to "pair up" its unpaired electrons; thus, they react with the unsaturated bonds of membrane lipids, denature proteins, and attack nucleic acids, resulting in cellular oxidative damage[189]. It has been suggested that oxidative stress plays an important role in many diseases, including DM, since hyperglycemia alone could not be exclusively responsible for the later complications associated with the disease[190]. ROS are considered an important independent risk factor that is developed in DM *via* what is known as "auto-oxidative glycosylation, a process which is relevant at elevated blood glucose level[191]. Hyperglycemia may also raise aldose reductase which depletes NADPH cell stores, thus perturbing defense system[192]. The elevated blood glucose level causes also non-enzymatic glycation of plasma proteins[193] leading to the production of more powerful oxidizing species[194]. Furthermore, it induces mitochondrial superoxide overproduction, which influences again the previous steps[195], creating what is known as "hyperglycemic memory"[196]. As oxidative stress plays a key role in insulin-resistance and β-cell dysfunction[197], ample of data allows the hypothesis that a viscous circle exists between hyper-insulinemia and free radicals that may be responsible for deterioration of insulin action[198], possibly *via* down-regulating insulin-mediated glucose uptake[199].

Given that antioxidants are favorably used as complementary agents in diabetic patients to reduce diabetic complications[200-203], attempts to discover antioxidants as useful drug candidates to combat diabetic complications are going on persistently.

Of the plants that exert their positive effects in experimental DM through their antioxidant characters are *Ficus carica via* restoring levels of fatty acids and vitamin E[204], as well as some Indian herbs, *viz*., *Allium sativum, Azadirachta indica, Momordica charantia,* and *Ocimum sanctum extracts,* which not only lowered the blood glucose level, but also inhibited the formation of lipid peroxides, reactivated the antioxidant enzymes, and restored levels of GSH and metals[124]. These results may authorize the use of the aforementioned herbs in the prevention of diabetes-associated complications. In addition, *Momordica grosvenori,* a traditional medicinal herb in China used as a substitute sugar for obese and diabetic patients, was tested in alloxan-induced diabetic mice[205]. The plant corrected the altered glucose level and effectively regulated the immune imbalance in diabetic mice. The authors assigned these effects to the plant-induced upregulation of heme oxygenase-1 (HO-1) protein, which has anti-inflammatory activities and antioxidant properties.

The ethanolic extract of *Scutellaria baicalensis*, as well, proves its antioxidant role in a STZ-induced diabetic model, and enhances the antidiabetic effect of metformin[206]. In addition, in a study on the antioxidant and antiglycation properties of some traditional Chinese medicine used to treat DM, *Aralia taibaiensis* outperformed other extracts in most of the assays except for the inhibition of early glycation products formation which was

mostly inhibited by *Acanthopanax senticosus* extract[207]. The antioxidant and antiglycation activities of these extracts were correlated with their saponin content[207]. The aqueous extract of *Albizzia lebbeck* was also verified for its antioxidant property using alloxan-induced diabetic rats[208]. The authors registered that the extract rescued all altered parameters caused by alloxan which confirmed the ability of the herb to resist the oxidative insult.

The hypoglycemic and hypolipidemic effects of *Lycium barbarum* fruit extract, its crude polysaccharides (LBP) extract and purified polysaccharide fractions (LBP-X), were documented in alloxan-induced diabetic rabbits[209]. Although the hypoglycemic effect of LBP-X surpassed the other extracts, yet the latter exhibited stronger antioxidant activity because crude extracts were identified to be rich in antioxidants (*e.g.*, carotenoids, riboflavin, ascorbic acid, thiamine, nicotinic acid). In Li[210] has isolated *Lycium barbarum* polysaccharides (LBP), which are identified as one of the active ingredients of the fruits, and tested its capacity to stand the oxidative insult using a STZ-induced hyperglycemic model. The author found again that the LBP reinstated the STZ-induced abnormal oxidative indices, results that are in line with another study by Wu *et al*[211], who also studied the antidiabetic effects of these polysaccharides, using rats with NIDDM. The authors found that LBP can control blood glucose and modulate the metabolism of glucose, leading to a significant improvement of oxidative stress markers (SOD, MDA), in addition to its ability to decrease DNA damage, possibly *via* leveling off oxidative stress. These findings point to the potential protective effect of LBP against deleterious oxidative stress, hence, preventing the development of diabetic complications.

Additionally, *Strobilanthes crispus* (*Acanthaceae*), which is used traditionally for the treatment of several ailments including DM, has shown antihyperglycemic and antilipidemic properties when tested in STZ-induced diabetic rats. The antioxidant effect of the herbal hot water extract (fermented and unfermented) contributed possibly to its and polyphenol contents[212].

Clinically, the valuable antioxidant effect of the herbal medicine, *Silybum marianum* seed extract (silymarin), was confirmed in a randomized, double-blind, placebo-controlled, clinical study of 51 type Ⅱ diabetic patients[213], where this extract induced a marked improvement in the glycemic profile of these patients.

In an attempt to study the effect of some herbal components against free radicals, Xiong *et al*[214] assessed the protective effect of puerarin, an isoflavone purified from Chinese herb radix of *Pueraria lobata*, on hydrogen peroxide (H_2O_2)-induced rat pancreatic islets damage. The results emphasize that puerarin can preserve islet cells from the ROS-induced damage. Likewise, the extract of *Plantago depressa var. montata*. was able to correct glucose and lipid homeostasis and to restore redox status in alloxan-induced diabetic mice, effects that are probably due to its antioxidant and free radical scavenging properties[215].

Another herbal drug evaluated for its hypoglycemic and anti-oxidant activities is the dried roots of *Morinda officinalis,* which was tested in STZ-treated rats and resulted in a decrease in fasting glucose and lipid peroxide levels, along with the restoration of the assessed redox indices. The study concluded that *Morinda officinalis* has anti-diabetic and antioxidant potentials[216]. Similarly, *Amaranthus esculantus* grain and oil fraction were found effective as both antioxidant and anti-diabetic, suggesting their beneficial effect in correcting hyperglycemia and preventing diabetic complications[217].

In the Turkish folkloric medicine *Gentiana olivieri* Griseb. (*Gentianaceae*) is used as a hypoglycemic plant, an effect that was verified by a recent study[218]. The hypoglycemic effect was attributed to its main active constituent, isoorientin, a compound that was documented for its favorable action on glucose homeostasis[219] partly *via* saving β-cells from oxidative damage by virtue of its potent antioxidant properties. Additionally, this compound may sensitize the insulin receptor to insulin or stimulate the stem cell of islets of Langerhans in pancreas of STZ-induced diabetic rats to restore plasma level of insulin[219]; however, these assumptions need to be tested.

Moreover, the ability of ginseng to scavenge free radicals is thought to add to its antidiabetic mechanisms[220]. Ginseng was found to decrease the rate of monosaccharide auto-oxidation, to elevate the activity of defence enzymes as SOD; and directly eliminate the superfluous free radicals. The same hold true for garlic (*Allium sativum* L., *Liliaceae*) which mediates its antidiabetic action by acts by its antioxidant character and by increasing insulin secretion[221].

The methanolic extract of *Phyllanthus amarus* (*Euphorbiaceae*), used traditionally in Indian herb medicine, was found to have a potent antioxidant activity added to its antihyperglycemic efficacy tested in alloxan-induced diabetic rats[222]. Other plants known for their antioxidant properties include *Capparis deciduas, Camellia sinensis, Emblica officinalis, Ficus bengalensis, Musa sapientum and Punica granatum*[151]. Additionally, the antidiabetic effects of fruit of *Vaccinium arctostaphylos* L. (Ericaceae), which is traditionally used in Iran for improving of health status of diabetic patients, was found to encounter several machinaries among which were the notable rising of the erythrocyte superoxide dismutase (57%), glutathione peroxidase (35%) and catalase (19%) activities of the alloxan-treated rats[223].

Hyperglycemia-induced aldose reductase activation results in the depletion of NADPH which is required for GSH reductase, hence, altering endogenous defense system. Therefore, inhibitors of aldose reductase could offer new approaches for the treatment of diabetes. Feng *et al*[224] reported in his study that some herbal active constituents, *viz*., flavonoid compounds and their derivates, have the ability to inhibit the activity of this enzyme, such as *quercetin, silymarin, puerarin,* and others. In addition, some *Salacia* root species possess this function, for example, the crude methanolic extract and ethyl acetate soluble fractions of *S. oblonga* showed inhibitory activity on rat lens-derived

aldose reductase[43]. In addition, the extract of *S. reticulata* stems, with its active constituent mangiferin, exhibited aldose reductase inhibitory activity[225], as well as the aqueous methanolic extract of *S. chinensis*[45].

CONCLUSION

From the previous data reviewed in the current article, it is obvious that herbs and/or their active constituents could attack several pathways of the hyperglycemic process. The multi-modes of their action allow them to outperform the conventional diabetic agents, besides the cost effectiveness and higher safety profile. These plants could be used as valuable therapeutic agents or as add-on conventional therapies for controlling glucose homeostasis. Although the evidenced-based therapeutic usage of many plants is scarce, the plants cited in this review are those reputed traditionally for their antidiabetic effect and that were verified, either experimentally or clinically.

REFERENCES

1 **López-Candales A**. Metabolic syndrome X: a comprehensive review of the pathophysiology and recommended therapy. *J Med* 2001; **32**: 283-300 [PMID: 11958275]
2 **Morphy R**, Kay C, Rankovic Z. From magic bullets to designed multiple ligands. *Drug Discov Today* 2004; **9**: 641–51 [DOI: 10.1016/S1359-6446(04)03163-0]
3 **Hui H**, Tang G, Go VLW. Hypoglycemic herbs and their action mechanisms. *Chin Med* 2009; **4**: 11 [DOI: 10.1186/1749-8546-4-11]
4 **Zimmet P**, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; **414**: 782–787 [DOI: 10.1038/414782a]
5 **Cohen P**, Goedert M. GSK3 inhibitors: development and therapeutic potential. *Nat Rev Drug Discov* 2004; **3**: 479–487 [DOI: 10.1038/nrd1415]
6 **Keith CT**, Borisy AA, Stockwell BR. Multicomponent therapeutics for networked systems. *Nat Rev Drug Discov* 2005; **4**: 71–78 [DOI: 10.1038/nrd1609]
7 **Li Y**, Peng G, Li Q, Wen S, Huang TH-W, Roufogalis BD, Yamahara J. Salacia oblonga improves cardiac fibrosis and inhibits postprandial hyperglycemia in obese Zucker rats. *Life Sci* 2004; **75**: 1735–1746 [DOI: 10.1016/j.lfs.2004.04.013]
8 **Kar A**, Choudhary BK, Bandyopadhyay NG. Comparative evaluation of hypoglycaemic activity of some Indian medicinal plants in alloxan diabetic rats. *J Ethnopharmacol* 2003; **84**: 105-108 [PMID: 12499084]
9 **Helmstädter A**. Antidiabetic drugs used in Europe prior to the discovery of insulin. *Pharmazie* 2007; **62**: 717-720 [PMID: 17944329]
10 **Abo KA**, Fred-Jaiyesimi AA, Jaiyesimi AE. Ethnobotanical studies of medicinal plants used in the management of diabetes mellitus in South Western Nigeria. *J Ethnopharmacol* 2008; **115**: 67-71 [PMID: 17950547 DOI: 10.1016/j.jep.2007.09.005]
11 **Witters LA**. The blooming of the French lilac. *J Clin Invest* 2001; **108**: 1105-1107 [PMID: 11602616 DOI: 10.1172/JCI14178]
12 **Caspary WF**. Sucrose malabsorption in man after ingestion of alpha-glucosidehydrolase inhibitor. *Lancet* 1978; **1**: 1231-1233 [PMID: 77996]
13 **Ramasubbu N**, Sundar K, Ragunath C, Rafi MM. Structural studies of a Phe256Trp mutant of human salivary alpha-amylase: implications for the role of a conserved water molecule in enzyme activity. *Arch Biochem Biophys* 2004; **421**: 115-124 [PMID: 14678792]
14 **Gao H**, Huang YN, Gao B, Li P, Inagaki C, Kawabata J. Inhibitory effect on a-glucosidase by Adhatoda vasica Nees. *Food Chemistry* 2008; **108**: 965–972 [DOI: 10.1016/j.foodchem.2007.12.002]
15 **Gao H**, Huang Y N, Xu P Y, Kawabata J. Inhibitory effect on a-glucosidase by the fruits of Terminalia chebula Retz. *Food Chemistry* 2007; **105**: 628–634 [DOI: 10.1016/j.foodchem.2007.04.023]
16 **Gao H**, Huang YN, Gao B, Xu PY, Inagaki C, Kawabata J. α-Glucosidase inhibitory effect by the flower buds of Tussilago farfara L. *Food Chemistry* 2008; **106**: 1195–1201 [DOI: 10.1016/j.foodchem.2007.07.064]
17 **Akowuah GA**, Zhari I, Norhayati I, Mariam A. HPLC and HPTLC densitometric determination of andrographolides and antioxidant potential of Andrographis paniculata. *J Food Comp Anal* 2006; **19**: 118–126 [DOI: 10.1016/j.jfca.2005.04.007]
18 **Subramanian R**, Asmawi MZ, Sadikun A. In vitro alpha-glucosidase and alpha-amylase enzyme inhibitory effects of Andrographis paniculata extract and andrographolide. *Acta Biochim Pol* 2008; **55**: 391-398 [PMID: 18511986]
19 **Loizzo MR**, Saab AM, Statti GA, Menichini F. Composition and alpha-amylase inhibitory effect of essential oils from Cedrus libani. *Fitoterapia* 2007; **78**: 323-326 [PMID: 17499940 DOI: 10.1016/j.fitote.2007.03.006]
20 **Zaoui A**, Cherrah Y, Alaoui K, Mahassine N, Amarouch H, Hassar M. Effects of Nigella sativa fixed oil on blood homeostasis in rat. *J Ethnopharmacol* 2002; **79**: 23-26 [PMID: 11744291]
21 **Le PM**, Benhaddou-Andaloussi A, Elimadi A, Settaf A, Cherrah Y, Haddad PS. The petroleum ether extract of Nigella sativa exerts lipid-lowering and insulin-sensitizing actions in the rat. *J Ethnopharmacol* 2004; **94**: 251-259 [PMID: 15325727 DOI: 10.1016/j.jep.2004.04.030]
22 **Benhaddou-Andaloussi A**, Martineau LC, Spoor D, Vuong T, Leduc C, Joly E , Burt A, Meddah B, Settaf A, Arnason JT, Prentki M, Haddad PS. Antidiabetic activity of Nigella sativa seed extract in cultured pancreatic β-cells, skeletal muscle cells, and adipocytes. *Pharmaceutical Biology* 2008; **46**: 96–104 [DOI: 10.1080/13880200701734810]
23 **Meddah B**, Ducroc R, El Abbes Faouzi M, Eto B, Mahraoui L, Benhaddou-Andaloussi A, Martineau LC, Cherrah Y, Haddad PS. Nigella sativa inhibits intestinal glucose absorption and improves glucose tolerance in rats. *J Ethnopharmacol* 2009; **121**: 419-424 [PMID: 19061948 DOI: 10.1016/j.jep.2008.10.040]
24 **Wright EM**, Loo DD, Hirayama BA, Turk E. Surprising versatility of Na+-glucose cotransporters: SLC5. *Physiology* (Bethesda) 2004; **19**: 370-376 [PMID: 15546855 DOI: 10.1152/physiol.00026.2004]
25 **Ducroc R**, Guilmeau S, Akasbi K, Devaud H, Buyse M, Bado A. Luminal leptin induces rapid inhibition of active intestinal absorption of glucose mediated by sodium-glucose cotransporter 1. *Diabetes* 2005; **54**: 348-354 [PMID: 15677491]
26 **Matsui T**, Ebuchi S, Kobayashi M, Fukui K, Sugita K, Terahara N, Matsumoto K. Anti-hyperglycemic effect of diacylated anthocyanin derived from Ipomoea batatas cultivar Ayamurasaki can be achieved through the alpha-glucosidase inhibitory action. *J Agric Food Chem* 2002; **50**: 7244-7248 [PMID: 12452639]
27 **Ortiz-Andrade RR**, García-Jiménez S, Castillo-España P, Ramírez-Avila G, Villalobos-Molina R, Estrada-Soto S. alpha-Glucosidase inhibitory activity of the methanolic extract from Tournefortia hartwegiana: an anti-hyperglycemic agent. *J Ethnopharmacol* 2007; **109**: 48-53 [PMID: 16920301 DOI: 10.1016/j.jep.2006.07.002]
28 **Ortiz-Andrade RR**, Rodríguez-López V, Garduño-Ramírez ML, Castillo-España P, Estrada-Soto S. Anti-diabetic effect on alloxanized and normoglycemic rats and some pharmacological evaluations of Tournefortia hartwegiana. *J Ethno-*

pharmacol 2005; **101**: 37-42 [PMID: 15894444 DOI: 10.1016/j.jep.2005.03.022]
29 **Davis SN**, Granner DK. Insulin. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed, New York: McGraw-Hill, 1996: 1487-1517
30 **Kameswara RB**, Kesavulu MM, Giri R, Appa RC. Anti-diabetic and hypolipidemic effects of Momordica cymbalaria Hook fruit powder in alloxan-diabetic rats. *J Etnhopharmacol* 1999; **67**: 103–109 [DOI: 10.1016/S0378-8741(99)00004-5]
31 **Stanely P**, Prince M, Menon VP. Hypoglycaemic and other related actions of Tinospora cordifolia roots in alloxan-induced diabetic rats. *J Ethnopharmacol* 2000; **70**: 9-15 [PMID: 10720784 DOI: 10.1016/S0378-8741(99)00136-1]
32 **Hawley SA**, Gadalla AE, Olsen GS, Hardie DG. The anti-diabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism. *Diabetes* 2002; **51**: 2420-2425 [PMID: 12145153 DOI: 10.2337/diabetes.51.8.2420]
33 **Li JM**, Che CT, Lau CB, Leung PS, Cheng CH. Inhibition of intestinal and renal Na+-glucose cotransporter by naringenin. *Int J Biochem Cell Biol* 2006; **38**: 985-995 [PMID: 16289850 DOI: 10.1016/j.biocel.2005.10.002]
34 **Asano N**, Ikeda K, Kasahara M, Arai Y, Kizu H. Glycosidase-inhibiting pyrrolidines and pyrrolizidines with a long side chain in Scilla peruviana. *J Nat Prod* 2004; **67**: 846-850 [PMID: 15165148 DOI: 10.1021/np0499721]
35 **Suresh Babu K**, Tiwari AK, Srinivas PV, Ali AZ, China Raju B, Rao JM. Yeast and mammalian alpha-glucosidase inhibitory constituents from Himalayan rhubarb Rheum emodi Wall.ex Meisson. *Bioorg Med Chem Lett* 2004; **14**: 3841-3845 [PMID: 15203173 DOI: 10.1016/j.bmcl.2004.04.062]
36 **Loizzo MR**, Saab AM, Tundis R, Menichini F, Bonesi M, Piccolo V, Statti GA, de Cindio B, Houghton PJ, Menichini F. In vitro inhibitory activities of plants used in Lebanon traditional medicine against angiotensin converting enzyme (ACE) and digestive enzymes related to diabetes. *J Ethnopharmacol* 2008; **119**: 109-116 [PMID: 18601990 DOI: 10.1016/j.jep.2008.06.003]
37 **Herrera-Arellano A**, Aguilar-Santamaría L, García-Hernández B, Nicasio-Torres P, Tortoriello J. Clinical trial of Cecropia obtusifolia and Marrubium vulgare leaf extracts on blood glucose and serum lipids in type 2 diabetics. *Phytomedicine* 2004; **11**: 561-566 [PMID: 15636168 DOI: 10.1016/j.phymed.2004.01.006]
38 **Omidbeygi R**. Usage and Production of Medical Plant, vol. 2. Iran: Tarahan Nashre Press, 1997: 210–216
39 **Zargari A**. Medicinal Plant, vol. 4. Iran: Tehran University Press, 1997: 59–64
40 **Zarzuelo A**, Risco S, Gámez MJ, Jimenez J, Cámara M, Martinez MA. Hypoglycemic action of Salvia lavandulifolia Vahl. spp. oxyodon: a contribution to studies on the mechanism of action. *Life Sci* 1990; **47**: 909-915 [PMID: 2215073]
41 **Hannan JM**, Ali L, Khaleque J, Akhter M, Flatt PR, Abdel-Wahab YH. Aqueous extracts of husks of Plantago ovata reduce hyperglycaemia in type 1 and type 2 diabetes by inhibition of intestinal glucose absorption. *Br J Nutr* 2006; **96**: 131-137 [PMID: 16870001]
42 **Shimoda H**, Kawamori S, KawaharaY. Effects of an aqueous extract of Salacia reticulata, a useful plant in Sri Lanka, on postprandial hyperglycemia in rats and humans. *Nihon Eiyo Shokuryo Gakkai Shi* 1998; **151**: 279–287 [DOI: 10.4327/jsnfs.51.279]
43 **Matsuda H**, Murakami T, Yashiro K, Yamahara J, Yoshikawa M. Antidiabetic principles of natural medicines. IV. Aldose reductase and qlpha-glucosidase inhibitors from the roots of Salacia oblonga Wall. (Celastraceae): structure of a new friedelane-type triterpene, kotalagenin 16-acetate. *Chem Pharm Bull* (Tokyo) 1999; **47**: 1725-1729 [PMID: 10748716]
44 **Matsuda H**, Morikawa T, Yoshikawa M. Antidiabetogenic constituents from several natural medicines. *Pure Appl Chem* 2002; **74**: 1301–1308 [DOI: 10.1351/pac200274071301]
45 **Yoshikawa M**, Pongpiriyadacha Y, Kishi A, Kageura T, Wang T, Morikawa T, Matsuda H. [Biological activities of Salacia chinensis originating in Thailand: the quality evaluation guided by alpha-glucosidase inhibitory activity]. *Yakugaku Zasshi* 2003; **123**: 871-880 [PMID: 14577333]
46 **Shah KA**, Patel MB, Patel RJ, Parmar PK. Mangifera indica (mango). *Pharmacogn Rev* 2010; **4**: 42-48 [PMID: 22228940 DOI: 10.4103/0973-7847.65325]
47 **Ojewole JA**. Antiinflammatory, analgesic and hypoglycemic effects of Mangifera indica Linn. (Anacardiaceae) stem-bark aqueous extract. *Methods Find Exp Clin Pharmacol* 2005; **27**: 547-554 [PMID: 16273134 DOI: 10.1358/mf.2005.27.8.928308]
48 **Hou W**, Li Y, Zhang Q, Wei X, Peng A, Chen L, Wei Y. Triterpene acids isolated from Lagerstroemia speciosa leaves as alpha-glucosidase inhibitors. *Phytother Res* 2009; **23**: 614-618 [PMID: 19107840 DOI: 10.1002/ptr.2661]
49 **Ali H**, Houghton PJ, Soumyanath A. alpha-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. *J Ethnopharmacol* 2006; **107**: 449-455 [PMID: 16678367 DOI: 10.1016/j.jep.2006.04.004]
50 **Liu X**, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P. Antidiabetic effect of Pycnogenol French maritime pine bark extract in patients with diabetes type II. *Life Sci* 2004; **75**: 2505-2513 [PMID: 15363656 DOI: 10.1016/j.lfs.2003.10.043]
51 **Schäfer A**, Högger P. Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol) effectively inhibit alpha-glucosidase. *Diabetes Res Clin Pract* 2007; **77**: 41-46 [PMID: 17098323 DOI: 10.1016/j.diabres.2006.10.011]
52 **Liu X**, Zhou HJ, Rohdewald P. French maritime pine bark extract Pycnogenol dose-dependently lowers glucose in type 2 diabetic patients. *Diabetes Care* 2004; **27**: 839 [PMID: 14988316]
53 **Rohdewald P**. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. *Int J Clin Pharmacol Ther* 2002; **40**: 158-168 [PMID: 11996210]
54 **Vats V**, Grover JK, Rathi SS. Evaluation of anti-hyperglycemic and hypoglycemic effect of Trigonella foenum-graecum Linn, Ocimum sanctum Linn and Pterocarpus marsupium Linn in normal and alloxanized diabetic rats. *J Ethnopharmacol* 2002; **79**: 95-100 [PMID: 11744301]
55 **Sharma RD**, Sarkar A, Hazra DK. Hypolipidemic effect of fenugreek seeds: a chronic study in non-insulin dependent diabetic patients. *Phytother Res* 1996; **10**: 332-334 [DOI: 10.1002/(SICI)1099-1573(199606)10: 4<332: : AID-PTR827>3.3.CO; 2-A]
56 **Vyas S**, Agrawal RP, Solanki P, Trivedi P. Analgesic and anti-inflammatory activities of Trigonella foenum-graecum (seed) extract. *Acta Pol Pharm* 2008; **65**: 473-476 [PMID: 19051589]
57 **Puri D**. Therapeutic potentials of fenugreek. *Indian J Physiol Pharmacol* 1998; **42**: 423-424 [PMID: 9741661]
58 **Suja Pandian R**, Anuradha CV, Viswanathan P. Gastroprotective effect of fenugreek seeds (Trigonella foenum graecum) on experimental gastric ulcer in rats. *J Ethnopharmacol* 2002; **81**: 393-397 [DOI: 10.1016/S0378-8741(02)00117-4]
59 **Sur P**, Das M, Gomes A, Vedasiromoni JR, Sahu NP, Banerjee S, Sharma RM, Ganguly DK. Trigonella foenum graecum (fenugreek) seed extract as an antineoplastic agent. *Phytother Res* 2001; **15**: 257-259 [PMID: 11351364]
60 **Riyad MA**, Abdul-Salam SA, Mohammad SS. Effect of fenugreek and lupine seeds on the development of experimental diabetes in rats. *Planta Med* 1988; **54**: 286-290 [PMID: 3222370 DOI: 10.1055/s-2006-962434]
61 **Raju J**, Gupta D, Rao AR, Yadava PK, Baquer NZ. Trigonellafoenum graecum (fenugreek) seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reversing the altered glycolytic, gluconeogenic and lipogenic enzymes.

Mol Cell Biochem 2001; **224**: 45-51 [PMID: 11693199 DOI: 10.1023/A]
62 **Park CH**, Noh JS, Tanaka T, Uebaba K, Cho EJ, Yokozawa T. The effects of corni fructus extract and its fractions against α-glucosidase inhibitory activities in vitro and sucrose tolerance in normal rats. *Am J Chin Med* 2011; **39**: 367-380 [PMID: 21476212 DOI: 10.1142/S0192415X11008889]
63 **Li Q**, Qu H. Study on the hypoglycemic activities and metabolism of alcohol extract of Alismatis Rhizoma. *Fitoterapia* 2012; **83**: 1046-1053 [PMID: 22613807 DOI: 10.1016/j.fitote.2012.05.009]
64 **Takahashi T**, Miyazawa M. Potent α-glucosidase inhibitors from safflower (Carthamus tinctorius L.) seed. *Phytother Res* 2012; **26**: 722-726 [PMID: 22021176 DOI: 10.1002/ptr.3622]
65 **Choo CY**, Sulong NY, Man F, Wong TW. Vitexin and isovitexin from the Leaves of Ficus deltoidea with in-vivo α-glucosidase inhibition. *J Ethnopharmacol* 2012; **142**: 776-781 [PMID: 22683902 DOI: 10.1016/j.jep.2012.05.062]
66 **Mahendran G**, Thamotharan G, Sengottuvelu S, Bai VN. Anti-diabetic activity of Swertia corymbosa (Griseb.) Wight ex C.B. Clarke aerial parts extract in streptozotocin induced diabetic rats. *J Ethnopharmacol* 2014; **151**: 1175-1183 [PMID: 24378350 DOI: 10.1016/j.jep.2013.12.032]
67 **Sapwarobol S**, Adisakwattana S, Changpeng S, Ratanawachirin W, Tanruttanawong K, Boonyarit W. Postprandial blood glucose response to grape seed extract in healthy participants: A pilot study. *Pharmacogn Mag* 2012; **8**: 192-196 [PMID: 23060692 DOI: 10.4103/0973-1296.99283]
68 **McCarty MF**. A chlorogenic acid-induced increase in GLP-1 production may mediate the impact of heavy coffee consumption on diabetes risk. *Med Hypotheses* 2005; **64**: 848-853 [PMID: 15694706 DOI: 10.1016/j.mehy.2004.03.037]
69 **Welsch CA**, Lachance PA, Wasserman BP. Dietary phenolic compounds: inhibition of Na+-dependent D-glucose uptake in rat intestinal brush border membrane vesicles. *J Nutr* 1989; **119**: 1698-1704 [PMID: 2600675]
70 **Johnston KL**, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am J Clin Nutr* 2003; **78**: 728-733 [PMID: 14522730]
71 **Hemmerle H**, Burger HJ, Below P, Schubert G, Rippel R, Schindler PW, Paulus E, Herling AW. Chlorogenic acid and synthetic chlorogenic acid derivatives: novel inhibitors of hepatic glucose-6-phosphate translocase. *J Med Chem* 1997; **40**: 137-145 [PMID: 9003513 DOI: 10.1021/jm9607360]
72 **Stümpel F**, Burcelin R, Jungermann K, Thorens B. Normal kinetics of intestinal glucose absorption in the absence of GLUT2: evidence for a transport pathway requiring glucose phosphorylation and transfer into the endoplasmic reticulum. *Proc Natl Acad Sci USA* 2001; **98**: 11330-11335 [PMID: 11562503 DOI: 10.1073/pnas.211357698]
73 **Santer R**, Hillebrand G, Steinmann B, Schaub J. Intestinal glucose transport: evidence for a membrane traffic-based pathway in humans. *Gastroenterology* 2003; **124**: 34-39 [PMID: 12512027 DOI: 10.1053/gast.2003.50009]
74 **Andrade-Cetto A**, Becerra-Jiménez J, Cárdenas-Vázquez R. Alfa-glucosidase-inhibiting activity of some Mexican plants used in the treatment of type 2 diabetes. *J Ethnopharmacol* 2008; **116**: 27-32 [PMID: 18082348 DOI: 10.1016/j.jep.2007.10.031]
75 **Andrade-Cetto A**, Wiedenfeld H. Hypoglycemic effect of Cecropia obtusifolia on streptozotocin diabetic rats. *J Ethnopharmacol* 2001; **78**: 145-149 [PMID: 11694359]
76 **Alonso-Castro AJ**, Miranda-Torres AC, González-Chávez MM, Salazar-Olivo LA. Cecropia obtusifolia Bertol and its active compound, chlorogenic acid, stimulate 2-NBDglucose uptake in both insulin-sensitive and insulin-resistant 3T3 adipocytes. *J Ethnopharmacol* 2008; **120**: 458-464 [PMID: 18948178 DOI: 10.1016/j.jep.2008.09.019]
77 **Shepherd PR**, Kahn BB. Glucose transporters and insulin action--implications for insulin resistance and diabetes mellitus. *N Engl J Med* 1999; **341**: 248-257 [PMID: 10413738 DOI: 10.1056/NEJM199907223410406]
78 **Gorovits N**, Cui L, Busik JV, Ranalletta M, Hauguel de-Mouzon S, Charron MJ. Regulation of hepatic GLUT8 expression in normal and diabetic models. *Endocrinology* 2003; **144**: 1703-1711 [PMID: 12697674 DOI: 10.1210/en.2002-220968]
79 **Kandror KV**, Pilch PF. Compartmentalization of protein traffic in insulin-sensitive cells. *Am J Physiol* 1996; **271**: E1-14 [PMID: 8760075]
80 **Berger J**, Biswas C, Vicario PP, Strout HV, Saperstein R, Pilch PF. Decreased expression of the insulin-responsive glucose transporter in diabetes and fasting. *Nature* 1989; **340**: 70-72 [PMID: 2739728 DOI: 10.1038/340070a0]
81 **Kang Y**, Kim HY. Glucose uptake-stimulatory activity of Amomi Semen in 3T3-L1 adipocytes. *J Ethnopharmacol* 2004; **92**: 103-105 [PMID: 15099855 DOI: 10.1016/j.jep.2004.02.003]
82 **Liu F**, Kim J, Li Y, Liu X, Li J, Chen X. An extract of Lagerstroemia speciosa L. has insulin-like glucose uptake-stimulatory and adipocyte differentiation-inhibitory activities in 3T3-L1 cells. *J Nutr* 2001; **131**: 2242-2247 [PMID: 11533261]
83 **Spoor DC**, Martineau LC, Leduc C, Benhaddou-Andaloussi A, Meddah B, Harris C, Burt A, Fraser MH, Coonishish J, Joly E, Cuerrier A, Bennett SA, Johns T, Prentki M, Arnason JT, Haddad PS. Selected plant species from the Cree pharmacopoeia of northern Quebec possess anti-diabetic potential. *Can J Physiol Pharmacol* 2006; **84**: 847-858 [PMID: 17111029 DOI: 10.1139/y06-018]
84 **Roffey B**, Atwal A, Kubow S. Cinnamon water extracts increase glucose uptake but inhibit adiponectin secretion in 3T3-L1 adipose cells. *Mol Nutr Food Res* 2006; **50**: 739-745 [PMID: 16835867 DOI: 10.1002/mnfr.200500253]
85 **Roffey BW**, Atwal AS, Johns T, Kubow S. Water extracts from Momordica charantia increase glucose uptake and adiponectin secretion in 3T3-L1 adipose cells. *J Ethnopharmacol* 2007; **112**: 77-84 [PMID: 17363205 DOI: 10.1016/j.jep.2007.02.003]
86 **Alonso-Castro AJ**, Salazar-Olivo LA. The anti-diabetic properties of Guazuma ulmifolia Lam are mediated by the stimulation of glucose uptake in normal and diabetic adipocytes without inducing adipogenesis. *J Ethnopharmacol* 2008; **118**: 252-256 [PMID: 18487028 DOI: 10.1016/j.jep.2008.04.007]
87 **Miura T**, Kubo M, Itoh Y, Iwamoto N, Kato M, Park SR, Ukawa Y, Kita Y, Suzuki I. Antidiabetic activity of Lyophyllum decastes in genetically type 2 diabetic mice. *Biol Pharm Bull* 2002; **25**: 1234-1237 [PMID: 12230127]
88 **Miura T**, Itoh Y, Kaneko T, Ueda N, Ishida T, Fukushima M, Matsuyama F, Seino Y. Corosolic acid induces GLUT4 translocation in genetically type 2 diabetic mice. *Biol Pharm Bull* 2004; **27**: 1103-1105 [PMID: 15256748]
89 **Takagi S**, Miura T, Ishibashi C, Kawata T, Ishihara E, Gu Y, Ishida T. Effect of corosolic acid on the hydrolysis of disaccharides. *J Nutr Sci Vitaminol* (Tokyo) 2008; **54**: 266-268 [PMID: 18635916]
90 **Choi SB**, Wha JD, Park S. The insulin sensitizing effect of homoisoflavone-enriched fraction in Liriope platyphylla Wang et Tang via PI3-kinase pathway. *Life Sci* 2004; **75**: 2653-2664 [PMID: 15369701 DOI: 10.1016/j.lfs.2004.04.039]
91 **Yu BC**, Hung CR, Chen WC, Cheng JT. Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. *Planta Med* 2003; **69**: 1075-1079 [PMID: 14750020 DOI: 10.1055/s-2003-45185]
92 **Lai DM**, Tu YK, Liu IM, Chen PF, Cheng JT. Mediation of beta-endorphin by ginsenoside Rh2 to lower plasma glucose in streptozotocin-induced diabetic rats. *Planta Med* 2006; **72**: 9-13 [PMID: 16450289 DOI: 10.1055/s-2005-916177]
93 **Liu IM**, Tzeng TF, Liou SS, Lan TW. Improvement of insulin sensitivity in obese Zucker rats by myricetin extracted from Abelmoschus moschatus. *Planta Med* 2007; **73**: 1054-1060 [PMID: 17694473 DOI: 10.1055/s-2007-981577]

94 **Anandharajan R**, Jaiganesh S, Shankernarayanan NP, Viswakarma RA, Balakrishnan A. In vitro glucose uptake activity of Aegles marmelos and Syzygium cumini by activation of Glut-4, PI3 kinase and PPARgamma in L6 myotubes. *Phytomedicine* 2006; **13**: 434-441 [PMID: 16716914 DOI: 10.1016/j.phymed.2005.03.008]

95 **Chattopadhyay RR**. Possible mechanism of antihyperglycemic effect of Azadirachta indica leaf extract. Part IV. *Gen Pharmacol* 1996; **27**: 431-434 [PMID: 8723520]

96 **Sangeetha MK**, Priya CD, Vasanthi HR. Anti-diabetic property of Tinospora cordifolia and its active compound is mediated through the expression of Glut-4 in L6 myotubes. *Phytomedicine* 2013; **20**: 246-248 [PMID: 23290487 DOI: 10.1016/j.phymed.2012.11.006]

97 **Omi T**, Brenig B, Spilar Kramer S, Iwamoto S, Stranzinger G, Neuenschwander S. Identification and characterization of novel peroxisome proliferator-activated receptor-gamma (PPAR-gamma) transcriptional variants in pig and human. *J Anim Breed Genet* 2005; **122** Suppl 1: 45-53 [PMID: 16130456]

98 **Mukherjee R**, Jow L, Croston GE, Paterniti JR. Identification, characterization, and tissue distribution of human peroxisome proliferator-activated receptor (PPAR) isoforms PPARgamma2 versus PPARgamma1 and activation with retinoid X receptor agonists and antagonists. *J Biol Chem* 1997; **272**: 8071-8076 [PMID: 9065481]

99 **Armoni M**, Kritz N, Harel C, Bar-Yoseph F, Chen H, Quon MJ, Karnieli E. Peroxisome proliferator-activated receptor-gamma represses GLUT4 promoter activity in primary adipocytes, and rosiglitazone alleviates this effect. *J Biol Chem* 2003; **278**: 30614-30623 [PMID: 12777391 DOI: 10.1074/jbc.M304654200]

100 **Nagashima K**, Lopez C, Donovan D, Ngai C, Fontanez N, Bensadoun A, Fruchart-Najib J, Holleran S, Cohn JS, Ramakrishnan R, Ginsberg HN. Effects of the PPARgamma agonist pioglitazone on lipoprotein metabolism in patients with type 2 diabetes mellitus. *J Clin Invest* 2005; **115**: 1323-1332 [PMID: 15841215 DOI: 10.1172/JCI23219]

101 **Rhee EJ**, Oh KW, Lee WY, Kim SY, Oh ES, Baek KH, Kang MI, Kim SW. Effects of two common polymorphisms of peroxisome proliferator-activated receptor-gamma gene on metabolic syndrome. *Arch Med Res* 2006; **37**: 86-94 [PMID: 16314192 DOI: 10.1016/j.arcmed.2005.04.008]

102 **Berthiaume M**, Sell H, Lalonde J, Gélinas Y, Tchernof A, Richard D, Deshaies Y. Actions of PPARgamma agonism on adipose tissue remodeling, insulin sensitivity, and lipemia in absence of glucocorticoids. *Am J Physiol Regul Integr Comp Physiol* 2004; **287**: R1116-R1123 [PMID: 15256367 DOI: 10.1152/ajpregu.00339.2004]

103 **Crawford P**. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial. *J Am Board Fam Med* 2009; **22**: 507-512 [PMID: 19734396 DOI: 10.3122/jabfm.2009.05.080093]

104 **Park MY**, Lee KS, Sung MK. Effects of dietary mulberry, Korean red ginseng, and banaba on glucose homeostasis in relation to PPAR-alpha, PPAR-gamma, and LPL mRNA expressions. *Life Sci* 2005; **77**: 3344-3354 [PMID: 15979095 DOI: 10.1016/j.lfs.2005.05.043]

105 **Rau O**, Wurglics M, Paulke A, Zitzkowski J, Meindl N, Bock A, Dingermann T, Abdel-Tawab M, Schubert-Zsilavecz M. Carnosic acid and carnosol, phenolic diterpene compounds of the labiate herbs rosemary and sage, are activators of the human peroxisome proliferator-activated receptor gamma. *Planta Med* 2006; **72**: 881-887 [PMID: 16858665 DOI: 10.1055/s-2006-946680]

106 **Rau O**, Wurglics M, Dingermann T, Abdel-Tawab M, Schubert-Zsilavecz M. Screening of herbal extracts for activation of the human peroxisome proliferator-activated receptor. *Pharmazie* 2006; **61**: 952-956 [PMID: 17152989]

107 **Banz WJ**, Iqbal MJ, Bollaert M, Chickris N, James B, Higginbotham DA, Peterson R, Murphy L. Ginseng modifies the diabetic phenotype and genes associated with diabetes in the male ZDF rat. *Phytomedicine* 2007; **14**: 681-689 [PMID: 17689944 DOI: 10.1016/j.phymed.2007.06.003]

108 **Li RW**, Douglas TD, Maiyoh GK, Adeli K, Theriault AG. Green tea leaf extract improves lipid and glucose homeostasis in a fructose-fed insulin-resistant hamster model. *J Ethnopharmacol* 2006; **104**: 24-31 [PMID: 16202550 DOI: 10.1016/j.jep.2005.08.045]

109 **Li RW**, Lin GD, Leach DN, Waterman PG, Myers SP. Inhibition of COXs and 5-LOX and activation of PPARs by Australian Clematis species (Ranunculaceae). *J Ethnopharmacol* 2006; **104**: 138-143 [PMID: 16207522 DOI: 10.1016/j.jep.2005.08.061]

110 **Atanasov AG**, Wang JN, Gu SP, Bu J, Kramer MP, Baumgartner L, Fakhrudin N, Ladurner A, Malainer C, Vuorinen A, Noha SM, Schwaiger S, Rollinger JM, Schuster D, Stuppner H, Dirsch VM, Heiss EH. Honokiol: a non-adipogenic PPARγ agonist from nature. *Biochim Biophys Acta* 2013; **1830**: 4813-4819 [PMID: 23811337 DOI: 10.1016/j.bbagen.2013.06.021]

111 **Iwaki M**, Matsuda M, Maeda N, Funahashi T, Matsuzawa Y, Makishima M, Shimomura I. Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. *Diabetes* 2003; **52**: 1655-1663 [PMID: 12829629]

112 **Hotta K**, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1595-1599 [PMID: 10845877]

113 **Ouchi N**, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; **100**: 2473-2476 [PMID: 10604883]

114 **Kondo H**, Shimomura I, Matsukawa Y, Kumada M, Takahashi M, Matsuda M, Ouchi N, Kihara S, Kawamoto T, Sumitsuji S, Funahashi T, Matsuzawa Y. Association of adiponectin mutation with type 2 diabetes: a candidate gene for the insulin resistance syndrome. *Diabetes* 2002; **51**: 2325-2328 [PMID: 12086969]

115 **Yamauchi T**, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; **7**: 941-946 [PMID: 11479627 DOI: 10.1038/90984]

116 **Maeda N**, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002; **8**: 731-737 [PMID: 12068289 DOI: 10.1038/nm724]

117 **Yamauchi T**, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002; **8**: 1288-1295 [PMID: 12368907 DOI: 10.1038/nm788]

118 **Berg AH**, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001; **7**: 947-953 [PMID: 11479628 DOI: 10.1038/90992]

119 **Karbowska J**, Kochan Z. Role of adiponectin in the regula-

tion of carbohydrate and lipid metabolism. *J Physiol Pharmacol* 2006; **57** Suppl 6: 103-113 [PMID: 17228091]
120 **Ludvik B**, Hanefeld M, Pacini G. Improved metabolic control by Ipomoea batatas (Caiapo) is associated with increased adiponectin and decreased fibrinogen levels in type 2 diabetic subjects. *Diabetes Obes Metab* 2008; **10**: 586-592 [PMID: 17645559 DOI: 10.1111/j.1463-1326.2007.00752.x]
121 **Naruszewicz M**, Laniewska I, Millo B, Dłużniewski M. Combination therapy of statin with flavonoids rich extract from chokeberry fruits enhanced reduction in cardiovascular risk markers in patients after myocardial infraction (MI). *Atherosclerosis* 2007; **194**: e179-e184 [PMID: 17320090 DOI: 10.1016/j.atherosclerosis.2006.12.032]
122 **Ahmed I**, Adeghate E, Sharma AK, Pallot DJ, Singh J. Effects of Momordica charantia fruit juice on islet morphology in the pancrease of the streptozotocin-diabetic rat. *Diabetes Res Clin Pract* 1998; **40**: 145–151 [DOI: 10.1016/S0168-8227(98)00022-9]
123 **Welihinda J**, Karunanayake EH, Sheriff MH, Jayasinghe KS. Effect of Momordica charantia on the glucose tolerance in maturity onset diabetes. *J Ethnopharmacol* 1986; **17**: 277-282 [PMID: 3807390]
124 **Welihinda J**, Karunanayake EH. Extra-pancreatic effects of Momordica charantia in rats. *J Ethnopharmacol* 1986; **17**: 247-255 [PMID: 3807387]
125 **Chandra A**, Mahdi AA, Singh RK, Mahdi F, Chander R. Effect of Indian herbal hypoglycemic agents on antioxidant capacity and trace elements content in diabetic rats. *J Med Food* 2008; **11**: 506-512 [PMID: 18800899 DOI: 10.1089/jmf.2007.0042]
126 **Ryu OH**, Lee J, Lee KW, Kim HY, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Effects of green tea consumption on inflammation, insulin resistance and pulse wave velocity in type 2 diabetes patients. *Diabetes Res Clin Pract* 2006; **71**: 356-358 [PMID: 16169629 DOI: 10.1016/j.diabres.2005.08.001]
127 **Utsunomiya H**, Yamakawa T, Kamei J, Kadonosono K, Tanaka S. Anti-hyperglycemic effects of plum in a rat model of obesity and type 2 diabetes, Wistar fatty rat. *Biomed Res* 2005; **26**: 193-200 [PMID: 16295695]
128 **Shimada T**, Nagai E, Harasawa Y, Watanabe M, Negishi K, Akase T, Sai Y, Miyamoto K, Aburada M. Salacia reticulata inhibits differentiation of 3T3-L1 adipocytes. *J Ethnopharmacol* 2011; **136**: 67-74 [PMID: 21511020 DOI: 10.1016/j.jep.2011.04.012]
129 **Gaw AC**, Ding Q, Levine RE, Gaw H. The clinical characteristics of possession disorder among 20 Chinese patients in the Hebei province of China. *Psychiatr Serv* 1998; **49**: 360-365 [PMID: 9525797]
130 **Habibuddin M**, Daghriri HA, Humaira T, Al Qahtani MS, Hefzi AA. Antidiabetic effect of alcoholic extract of Caralluma sinaica L. on streptozotocin-induced diabetic rabbits. *J Ethnopharmacol* 2008; **117**: 215-220 [PMID: 18359177 DOI: 10.1016/j.jep.2008.01.021]
131 **Attele AS**, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS, Yuan CS. Antidiabetic effects of Panax ginseng berry extract and the identification of an effective component. *Diabetes* 2002; **51**: 1851-1858 [PMID: 12031973]
132 **Hasegawa H**, Matsumiya S, Murakami C, Kurokawa T, Kasai R, Ishibashi S, Yamasaki K. Interactions of ginseng extract, ginseng separated fractions, and some triterpenoid saponins with glucose transporters in sheep erythrocytes. *Planta Med* 1994; **60**: 153-157 [PMID: 8202566 DOI: 10.1055/s-2006-959440]
133 **Suzuki Y**, Ito Y, Konno C, Furuya T. [Effects of tissue cultured ginseng on gastric secretion and pepsin activity]. *Yakugaku Zasshi* 1991; **111**: 770-774 [PMID: 1806658]
134 **Welihinda J**, Arvidson G, Gylfe E, Hellman B, Karlsson E. The insulin-releasing activity of the tropical plant momordica charantia. *Acta Biol Med Ger* 1982; **41**: 1229-1240 [PMID: 6765165]
135 **Maiti R**, Das UK, Ghosh D. Attenuation of hyperglycemia and hyperlipidemia in streptozotocin-induced diabetic rats by aqueous extract of seed of Tamarindus indica. *Biol Pharm Bull* 2005; **28**: 1172-1176 [PMID: 15997092]
136 **Sole SS**, Srinivasan BP. Aqueous extract of tamarind seeds selectively increases glucose transporter-2, glucose transporter-4, and islets' intracellular calcium levels and stimulates β-cell proliferation resulting in improved glucose homeostasis in rats with streptozotocin-induced diabetes mellitus. *Nutr Res* 2012; **32**: 626-636 [PMID: 22935346 DOI: 10.1016/j.nutres.2012.06.015]
137 **Eidi A**, Eidi M, Sokhteh M. Effect of fenugreek (Trigonella foenum-graecum L) seeds on serum parameters in normal and streptozotocin-induced diabetic rats. *Nutr Res* 2007; **27**: 728–733[DOI: 10.1016/j.nutres.2007.09.006]
138 **Eidi A**, Eidi M, Esmaeili E. Antidiabetic effect of garlic (Allium sativum L.) in normal and streptozotocin-induced diabetic rats. *Phytomedicine* 2006; **13**: 624-629 [PMID: 17085291 DOI: 10.1016/j.phymed.2005.09.010]
139 **Chang ML**, Johnson MA. Effect of garlic on carbohydrate metabolism and lipid synthesis in rats. *J Nutr* 1980; **110**: 931-936 [PMID: 6989965]
140 **Mathew PT**, Augusti KT. Studies on the effect of allicin (diallyl disulphide-oxide) on alloxan diabetes. I. Hypoglycaemic action and enhancement of serum insulin effect and glycogen synthesis. *Indian J Biochem Biophys* 1973; **10**: 209-212 [PMID: 4792931]
141 **Augusti KT**. Therapeutic values of onion (Allium cepa L.) and garlic (Allium sativum L.). *Indian J Exp Biol* 1996; **34**: 634-640 [PMID: 8979497]
142 **Islam MS**, Choi H. Comparative effects of dietary ginger (Zingiber officinale) and garlic (Allium sativum) investigated in a type 2 diabetes model of rats. *J Med Food* 2008; **11**: 152-159 [PMID: 18361751 DOI: 10.1089/jmf.2007.634]
143 **Islam MS**, Choi H. Dietary red chilli (Capsicum frutescens L.) is insulinotropic rather than hypoglycemic in type 2 diabetes model of rats. *Phytother Res* 2008; **22**: 1025-1029 [PMID: 18668490 DOI: 10.1002/ptr.2417]
144 **Hannan JM**, Marenah L, Ali L, Rokeya B, Flatt PR, Abdel-Wahab YH. Ocimum sanctum leaf extracts stimulate insulin secretion from perfused pancreas, isolated islets and clonal pancreatic beta-cells. *J Endocrinol* 2006; **189**: 127-136 [PMID: 16614387 DOI: 10.1677/joe.1.06615]
145 **Hannan JM**, Marenah L, Ali L, Rokeya B, Flatt PR, Abdel-Wahab YH. Insulin secretory actions of extracts of Asparagus racemosus root in perfused pancreas, isolated islets and clonal pancreatic beta-cells. *J Endocrinol* 2007; **192**: 159-168 [PMID: 17210753 DOI: 10.1677/joe.1.07084]
146 **Jeppesen PB**, Gregersen S, Alstrup KK, Hermansen K. Stevioside induces antihyperglycaemic, insulinotropic and glucagonostatic effects in vivo: studies in the diabetic Goto-Kakizaki (GK) rats. *Phytomedicine* 2002; **9**: 9-14 [PMID: 11924770 DOI: 10.1078/0944-7113-00081]
147 **Eno AE**, Ofem OE, Nku CO, Ani EJ, Itam EH. Stimulation of insulin secretion by Viscum album (mistletoe) leaf extract in streptozotocin-induced diabetic rats. *Afr J Med Med Sci* 2008; **37**: 141-147 [PMID: 18939397]
148 **Abdel-Zaher AO**, Salim SY, Assaf MH, Abdel-Hady RH. Antidiabetic activity and toxicity of Zizyphus spina-christi leaves. *J Ethnopharmacol* 2005; **101**: 129-138 [PMID: 16009520 DOI: 10.1016/j.jep.2005.04.007]
149 **Puri D**. The insulinotropic activity of a Nepalese medicinal plant Biophytum sensitivum: preliminary experimental study. *J Ethnopharmacol* 2001; **78**: 89-93 [PMID: 11585694]
150 **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**: 163-173 [PMID: 18398493 DOI: 10.3164/jcbn.40.163]
151 **Patel D**, Prasad S, Kumar R, Hemalatha S. An overview on antidiabetic medicinal plants having insulin mimetic proper-

ty. *Asian Pac J Trop Biomed* 2012; **2**: 320-330 [PMID: 23569923 DOI: 10.1016/S2221-1691(12)60032-X]
152 **Hsu YS**, Kuo YH, Cheng HL, Flatt PR, Liu HK. Schizandra arisanensis extract attenuates cytokine-mediated cytotoxicity in insulin-secreting cells. *World J Gastroenterol* 2012; **18**: 6809-6818 [PMID: 23239919 DOI: 10.3748/wjg.v18.i46.6809]
153 **Larner J**, Allan G, Kessler C, Reamer P, Gunn R, Huang LC. Phosphoinositol glycan derived mediators and insulin resistance. Prospects for diagnosis and therapy. *J Basic Clin Physiol Pharmacol* 1998; **9**: 127-137 [PMID: 10212830]
154 **Ostlund RE**, McGill JB, Herskowitz I, Kipnis DM, Santiago JV, Sherman WR. D-chiro-inositol metabolism in diabetes mellitus. *Proc Natl Acad Sci USA* 1993; **90**: 9988-9992 [PMID: 8234346]
155 **Fonteles MC**, Huang LC, Larner J. Infusion of pH 2.0 D-chiro-inositol glycan insulin putative mediator normalizes plasma glucose in streptozotocin diabetic rats at a dose equivalent to insulin without inducing hypoglycaemia. *Diabetologia* 1996; **39**: 731-734 [PMID: 8781770]
156 **Kennington AS**, Hill CR, Craig J, Bogardus C, Raz I, Ortmeyer HK, Hansen BC, Romero G, Larner J. Low urinary chiro-inositol excretion in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1990; **323**: 373-378 [PMID: 2370888 DOI: 10.1056/NEJM199008093230603]
157 **Ortmeyer HK**, Huang LC, Zhang L, Hansen BC, Larner J. Chiroinositol deficiency and insulin resistance. II. Acute effects of D-chiroinositol administration in streptozotocin-diabetic rats, normal rats given a glucose load, and spontaneously insulin-resistant rhesus monkeys. *Endocrinology* 1993; **132**: 646-651 [PMID: 8425484 DOI: 10.1210/endo.132.2.8425484]
158 **Larner J**. D-chiro-inositol--its functional role in insulin action and its deficit in insulin resistance. *Int J Exp Diabetes Res* 2002; **3**: 47-60 [PMID: 11900279]
159 **Xia T**, Wang Q. D-chiro-inositol found in Cucurbita ficifolia (Cucurbitaceae) fruit extracts plays the hypoglycaemic role in streptozocin-diabetic rats. *J Pharm Pharmacol* 2006; **58**: 1527-1532 [PMID: 17132216 DOI: 10.1211/jpp.58.10.0014]
160 **Yao Y**, Shan F, Bian J, Chen F, Wang M, Ren G. D-chiro-inositol-enriched tartary buckwheat bran extract lowers the blood glucose level in KK-Ay mice. *J Agric Food Chem* 2008; **56**: 10027-10031 [PMID: 18921966 DOI: 10.1021/jf801879m]
161 **Scheen AJ**. Glucagon-like peptide-1 (GLP-1), new target for the treatment of type 2 diabetes. *Rev Med Liege* 2007; **62**: 217-221 [PMID: 17566392]
162 **Scheen AJ**, Radermecker RP, Philips JC, Paquot N. Incretin mimetics and incretin enhancers for the treatment of type 2 diabetes. *Rev Med Suisse* 2007; **3**: 1884, 1886-1888 [PMID: 17896662]
163 **Urías-Silvas JE**, Cani PD, Delmée E, Neyrinck A, López MG, Delzenne NM. Physiological effects of dietary fructans extracted from Agave tequilana Gto. and Dasylirion spp. *Br J Nutr* 2008; **99**: 254-261 [PMID: 17711612 DOI: 10.1017/S0007114507795338]
164 **Ribnicky DM**, Poulev A, Watford M, Cefalu WT, Raskin I. Antihyperglycemic activity of Tarralin, an ethanolic extract of Artemisia dracunculus L. *Phytomedicine* 2006; **13**: 550-557 [PMID: 16920509 DOI: 10.1016/j.phymed.2005.09.007]
165 **Park SM**, Hong SM, Sung SR, Lee JE, Kwon DY. Extracts of Rehmanniae radix, Ginseng radix and Scutellariae radix improve glucose-stimulated insulin secretion and beta-cell proliferation through IRS2 induction. *Genes Nutr* 2008; **2**: 347-351 [PMID: 18850229 DOI: 10.1007/s12263-007-0065-y]
166 **Li CH**, Chung D, Doneen BA. Isolation, characterization and opiate activity of b-endorphin from human pituitary glands. *Biochem Biophys Res Commun* 1976; **72**: 1542–1547 [DOI: 10.1016/S0006-291X(76)80189-1]
167 **Viveros OH**, Diliberto EJ, Hazum E, Chang KJ. Opiate-like materials in the adrenal medulla: evidence for storage and secretion with catecholamines. *Mol Pharmacol* 1979; **16**: 1101-1108 [PMID: 530253]
168 **Curry DL**, Li CH. Stimulation of insulin secretion by beta endorphin (1-27 and 1-31). *Life Sci* 1987; **40**: 2053–2058 [DOI: 10.1016/0024-3205(87)90097-X]
169 **Giugliano D**, Cozzolino D, Salvatore T, Ceriello A, Torella R. Dual effect of beta-endorphin on insulin secretion in man. *Horm Metab Res* 1987; **19**: 502-503 [PMID: 2962921 DOI: 10.1055/s-2007-1011863]
170 **Khawaja XZ**, Green IC. Dual action of beta-endorphin on insulin release in genetically obese and lean mice. *Peptides* 1978; **12**: 227-233 [PMID: 2067974]
171 **Paolisso G**, Giugliano D, Scheen AJ, Franchimont P, D'Onofrio F, Lefèbvre PJ. Primary role of glucagon release in the effect of beta-endorphin on glucose homeostasis in normal man. *Acta Endocrinol* (Copenh) 1987; **115**: 161-169 [PMID: 2885994]
172 **Liu IM**, Cheng JT. Mediation of Endogenous β-Endorphin in the Plasma Glucose-Lowering Action of Herbal Products Observed in Type 1-Like Diabetic Rats. *Evid Based Complement Alternat Med* 2011; **2011**: 987876 [PMID: 19095661 DOI: 10.1093/ecam/nen078]
173 **Cheng JT**, Liu IM, Kuo DH, Lin MT. Stimulatory effect of phenylephrine on the secretion of beta-endorphin from rat adrenal medulla in vitro. *Auton Neurosci* 2001; **93**: 31-35 [PMID: 11695703]
174 **Herbert JM**, Augereau JM, Gleye J, Maffrand JP. Chelerythrine is a potent and specific inhibitor of protein kinase C. *Biochem Biophys Res Commun* 1990; **172**: 993-999 [PMID: 2244923]
175 **Toullec D**, Pianetti P, Coste H, Bellevergue P, Grand-Perret T, Ajakane M, Baudet V, Boissin P, Boursier E, Loriolle F. The bisindolylmaleimide GF 109203X is a potent and selective inhibitor of protein kinase C. *J Biol Chem* 1991; **266**: 15771-15781 [PMID: 1874734]
176 **Hsu CT**, Liu IM, Cheng JT. Increase of beta-endorphin biosynthesis in the adrenal gland of streptozotocin-induced diabetic rats. *Neurosci Lett* 2002; **318**: 57-60 [PMID: 11796185]
177 **Cheng JT**, Liu IM, Chi TC, Tzeng TF, Lu FH, Chang CJ. Plasma glucose-lowering effect of tramadol in streptozotocin-induced diabetic rats. *Diabetes* 2001; **50**: 2815-2821 [PMID: 11723065]
178 **Hsu FL**, Chen YC, Cheng JT. Caffeic acid as active principle from the fruit of Xanthium strumarium to lower plasma glucose in diabetic rats. *Planta Med* 2000; **66**: 228-230 [PMID: 10821047 DOI: 10.1055/s-2000-8561]
179 **Cheng JT**, Liu IM, Tzeng TF, Chen WC, Hayakawa S, Yamamoto T. Release of beta-endorphin by caffeic acid to lower plasma glucose in streptozotocin-induced diabetic rats. *Horm Metab Res* 2003; **35**: 251-258 [PMID: 12778369 DOI: 10.1055/s-2003-39482]
180 **Hsu JH**, Liou SS, Yu BC, Cheng JT, Wu YC. Activation of alpha1A-adrenoceptor by andrographolide to increase glucose uptake in cultured myoblast C2C12 cells. *Planta Med* 2004; **70**: 1230-1233 [PMID: 15643563 DOI: 10.1055/s-2004-835857]
181 **Yu BC**, Chang CK, Su CF, Cheng JT. Mediation of beta-endorphin in andrographolide-induced plasma glucose-lowering action in type I diabetes-like animals. *Naunyn Schmiedebergs Arch Pharmacol* 2008; **377**: 529-540 [PMID: 18080810 DOI: 10.1007/s00210-007-0240-0]
182 **Liu IM**, Liou SS, Cheng JT. Mediation of beta-endorphin by myricetin to lower plasma glucose in streptozotocin-induced diabetic rats. *J Ethnopharmacol* 2006; **104**: 199-206 [PMID: 16203117 DOI: 10.1016/j.jep.2005.09.001]
183 **Niu HS**, Hsu FL, Liu IM, Cheng JT. Increase of beta-endorphin secretion by syringin, an active principle of Eleutherococcus senticosus, to produce antihyperglycemic action in type 1-like diabetic rats. *Horm Metab Res* 2007; **39**: 894-898 [PMID: 18075969 DOI: 10.1055/s-2007-993154]
184 **Liu IM**, Chi TC, Hsu FL, Chen CF, Cheng JT. Isoferulic acid as active principle from the rhizoma of Cimicifuga dahurica

to lower plasma glucose in diabetic rats. *Planta Med* 1999; **65**: 712-714 [PMID: 10630111 DOI: 10.1055/s-1999-14048]
185 **Liu IM**, Tsai CC, Lai TY, Cheng JT. Stimulatory effect of isoferulic acid on alpha1A-adrenoceptor to increase glucose uptake into cultured myoblast C2C12 cell of mice. *Auton Neurosci* 2001; **88**: 175-180 [PMID: 11474559]
186 **Liu IM**, Hsu FL, Chen CF, Cheng JT. Antihyperglycemic action of isoferulic acid in streptozotocin-induced diabetic rats. *Br J Pharmacol* 2000; **129**: 631-636 [PMID: 10683186 DOI: 10.1038/sj.bjp.0703082]
187 **Chen WC**, Hayakawa S, Yamamoto T, Su HC, Liu IM, Cheng JT. Mediation of beta-endorphin by the isoflavone puerarin to lower plasma glucose in streptozotocin-induced diabetic rats. *Planta Med* 2004; **70**: 113-116 [PMID: 14994187 DOI: 10.1055/s-2004-815486]
188 **Chandra M**, Chandra N, Agrawal R, Kumar A, Ghatak A, Pandey VC. The free radical system in ischemic heart disease. *Int J Cardiol* 1994; **43**: 121-125 [PMID: 8181866]
189 **Papas AM**. Determinants of antioxidant status in humans. *Lipids* 1996; **31** Suppl: S77-S82 [PMID: 8729098]
190 **Wolff SP**. Diabetes mellitus and free radicals. Free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. *Br Med Bull* 1993; **49**: 642-652 [PMID: 8221029]
191 **Mooradian AD**, Lung CC, Pinnas JL. Glycosylation enhances malondialdehyde binding to proteins. *Free Radic Biol Med* 1996; **21**: 699-701 [PMID: 8891672]
192 **Tames FJ**, Mackness MI, Arrol S, Laing I, Durrington PN. Non-enzymatic glycation of apo-lipoprotein B in the sera of diabetic and non-diabetic subjects. *Atherosclerosis* 1992; **93**: 237 [DOI: 10.1016/0021-9150(92)90260-N]
193 **Hunt JV**, Bottoms MA, Mitchinson MJ. Oxidative alterations in the experimental glycation model of diabetes mellitus are due to protein-glucose adduct oxidation. Some fundamental differences in proposed mechanisms of glucose oxidation and oxidant production. *Biochem J* 1993; **291** (Pt 2): 529-535 [PMID: 8484733]
194 **Nishikawa T**, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giardino I, Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000; **404**: 787-790 [PMID: 10783895 DOI: 10.1038/35008121]
195 **Taguchi T**, Brownlee M In: Pickkup JC, Williams G. (Eds). The biochemical mechanisms of diabetic tissue damage. Text Book of Diabetes. Oxford: Blackwell Science, 2003: 1-47
196 **Donnini D**, Zambito AM, Perrella G, Ambesi-Impiombato FS, Curcio F. Glucose may induce cell death through a free radical-mediated mechanism. *Biochem Biophys Res Commun* 1996; **219**: 412-417 [PMID: 8605001 DOI: 10.1006/bbrc.1996.0247]
197 **Ceolotto G**, Bevilacqua M, Papparella I, Baritono E, Franco L, Corvaja C, Mazzoni M, Semplicini A, Avogaro A. Insulin generates free radicals by an NAD(P)H, phosphatidylinositol 3'-kinase-dependent mechanism in human skin fibroblasts ex vivo. *Diabetes* 2004; **53**: 1344-1351 [PMID: 15111505]
198 **Levy J**, Gavin JR, Sowers JR. Diabetes mellitus: a disease of abnormal cellular calcium metabolism? *Am J Med* 1994; **96**: 260-273 [PMID: 8154515]
199 **Wohaieb SA**, Godin DV. Alterations in free radical tissue-defense mechanisms in streptozocin-induced diabetes in rat. Effects of insulin treatment. *Diabetes* 1987; **36**: 1014-1018 [PMID: 3301471 DOI: 10.2337/diab.36.9.1014]
200 **Sardesai VM**. Role of antioxidants in health maintenance. *Nutr Clin Pract* 1995; **10**: 19-25 [PMID: 7898413]
201 **Gibaldi M**. Antioxidant vitamins and health. *J Clin Pharmacol* 1996; **36**: 1093-1099 [PMID: 9013364]
202 **Gökkusu C**, Palanduz S, Ademoğlu E, Tamer S. Oxidant and antioxidant systems in niddm patients: influence of vitamin E supplementation. *Endocr Res* 2001; **27**: 377-386 [PMID: 11678585]
203 **Garcia-Medina JJ**, Pinazo-Duran MD, Garcia-Medina M, Zanon-Moreno V, Pons-Vazquez S. A 5-year follow-up of antioxidant supplementation in type 2 diabetic retinopathy. *Eur J Ophthalmol* 2011; **21**: 637-643 [PMID: 21218388 DOI: 10.5301/EJO.2010.6212]
204 **Pèrez C**, Canal JR, Torres MD. Experimental diabetes treated with ficus carica extract: effect on oxidative stress parameters. *Acta Diabetol* 2003; **40**: 3-8 [PMID: 12682822 DOI: 10.1007/s005920300001]
205 **Song F**, Chen W, Jia W, Yao P, Nussler AK, Sun X, Liu L. A natural sweetener, Momordica grosvenori, attenuates the imbalance of cellular immune functions in alloxan-induced diabetic mice. *Phytother Res* 2006; **20**: 552-560 [PMID: 16619338 DOI: 10.1002/ptr.1903]
206 **Waisundara VY**, Hsu A, Huang D, Tan BK. Scutellaria baicalensis enhances the anti-diabetic activity of metformin in streptozotocin-induced diabetic Wistar rats. *Am J Chin Med* 2008; **36**: 517-540 [PMID: 18543386 DOI: 10.1142/S0192415X08005953]
207 **Xi M**, Hai C, Tang H, Chen M, Fang K, Liang X. Antioxidant and antiglycation properties of total saponins extracted from traditional Chinese medicine used to treat diabetes mellitus. *Phytother Res* 2008; **22**: 228-237 [PMID: 17886226 DOI: 10.1002/ptr.2297]
208 **Resmi CR**, Venukumar MR, Latha MS. Antioxidant activity of Albizzia lebbeck (Linn.) Benth. in alloxan diabetic rats. *Indian J Physiol Pharmacol* 2006; **50**: 297-302 [PMID: 17193903]
209 **Luo Q**, Cai Y, Yan J, Sun M, Corke H. Hypoglycemic and hypolipidemic effects and antioxidant activity of fruit extracts from Lycium barbarum. *Life Sci* 2004; **76**: 137-149 [PMID: 15519360 DOI: 10.1016/j.lfs.2004.04.056]
210 **Li XM**. Protective effect of Lycium barbarum polysaccharides on streptozotocin-induced oxidative stress in rats. *Int J Biol Macromol* 2007; **40**: 461-465 [PMID: 17166579 DOI: 10.1016/j.ijbiomac.2006.11.002]
211 **Wu H**, Guo H, Zhao R. Effect of Lycium barbarum polysaccharide on the improvement of antioxidant ability and DNA damage in NIDDM rats. *Yakugaku Zasshi* 2006; **126**: 365-371 [PMID: 16679745]
212 **Fadzelly AB**, Asmah R, Fauziah O. Effects of Strobilanthes crispus tea aqueous extracts on glucose and lipid profile in normal and streptozotocin-induced hyperglycemic rats. *Plant Foods Hum Nutr* 2006; **61**: 7-12 [PMID: 16688478 DOI: 10.1007/s11130-006-0002-z]
213 **Huseini HF**, Larijani B, Heshmat R, Fakhrzadeh H, Radjabipour B, Toliat T, Raza M. The efficacy of Silybum marianum (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial. *Phytother Res* 2006; **20**: 1036-1039 [PMID: 17072885 DOI: 10.1002/ptr.1988]
214 **Xiong S**, Melton LD, Easteal AJ, Siew D. Stability and antioxidant activity of black currant anthocyanins in solution and encapsulated in glucan gel. *J Agric Food Chem* 2006; **54**: 6201-6208 [PMID: 16910708 DOI: 10.1021/jf060889o]
215 **Wu FH**, Liang JY, Yu P, Cai SF. Studies on the hypoglycemia and lipids regulating effects of Plantago depressa var. montata. *Zhongguo Zhongyao Zazhi* 2005; **30**: 1179-1183 [PMID: 16201696]
216 **Soon YY**, Tan BK. Evaluation of the hypoglycemic and antioxidant activities of Morinda officinalis in streptozotocin-induced diabetic rats. *Singapore Med J* 2002; **43**: 077-085 [PMID: 11993894]
217 **Kim HK**, Kim MJ, Cho HY, Kim EK, Shin DH. Antioxidative and anti-diabetic effects of amaranth (Amaranthus esculantus) in streptozotocin-induced diabetic rats. *Cell Biochem Funct* 2006; **24**: 195-199 [PMID: 16634092 DOI: 10.1002/cbf.1210]
218 **Sezik E**, Aslan M, Yesilada E, Ito S. Hypoglycaemic activity of Gentiana olivieri and isolation of the active constituent through bioassay-directed fractionation techniques. *Life*

Sci 2005; **76**: 1223-1238 [PMID: 15642593 DOI: 10.1016/j.lfs.2004.07.024]
219 **Orhan DD**, Aslan M, Aktay G, Ergun E, Yesilada E, Ergun F. Evaluation of hepatoprotective effect of Gentiana olivieri herbs on subacute administration and isolation of active principle. *Life Sci* 2003; **72**: 2273-2283 [PMID: 12628447]
220 **Xie ZC**, Qian ZK, Liu ZW. Effect of ginseng on antiperoxidate injury in myocardium and erythrocytes in streptozocin-induced diabetic rats. *Zhongguo Zhongxiyi Jiehe Zazhi* 1993; **13**: 289-290, 262 [PMID: 8219682]
221 **Anwar MM**, Meki AR. Oxidative stress in streptozotocin-induced diabetic rats: effects of garlic oil and melatonin. *Comp Biochem Physiol A Mol Integr Physiol* 2003; **135**: 539-547 [PMID: 12890544]
222 **Raphael KR**, Sabu MC, Kuttan R. Hypoglycemic effect of methanol extract of Phyllanthus amarus Schum & amp; Thonn on alloxan induced diabetes mellitus in rats and its relation with antioxidant potential. *Indian J Exp Biol* 2002; **40**: 905-909 [PMID: 12597020]
223 **Feshani AM**, Kouhsari SM, Mohammadi S. Vaccinium arctostaphylos, a common herbal medicine in Iran: molecular and biochemical study of its antidiabetic effects on alloxan-diabetic Wistar rats. *J Ethnopharmacol* 2011; **133**: 67-74 [PMID: 20850514 DOI: 10.1016/j.jep.2010.09.002]
224 **Feng CG**, Zhang LX, Liu X. [Progress in research of aldose reductase inhibitors in traditional medicinal herbs]. *Zhongguo Zhongyao Zazhi* 2005; **30**: 1496-1500 [PMID: 16335816]
225 **Yoshikawa M**, Nishida N, Shimoda H, Takada M, Kawahara Y, Matsuda H. Polyphenol constituents from Salacia species: quantitative analysis of mangiferin with alpha-glucosidase and aldose reductase inhibitory activities. *Yakugaku Zasshi* 2001; **121**: 371-378 [PMID: 11360491]

P- Reviewers: Michael K, Sasaoka T, Teeter JG
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Wu HL

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com