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Traditional Medicinal Herbs for the Management of Diabetes and its Complications: An Evidence-Based Review

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ABSTRACT

Diabetes mellitus is a complex metabolic disease associated with impaired insulin secretion, developing insulin resistance as well as β -cell dysfunction, that leads to abnormal glucose, protein and lipid metabolism, inflammatory responses and oxidative damages. Traditional medicines suggest a wide range of remedies for the management of symptomatology associated with chronic disorders including diabetes mellitus. The aim of the present study is to elicit the most popular traditionally used medicinal plants for diabetes and review literatures in order to scientifically evaluate their efficacy and safety in diabetes mellitus and its complications. In addition, their molecular and cellular mechanisms of action along with active phytochemical agents were highlighted. The findings demonstrated that traditional herbal remedies perform their antidiabetic potential through different cellular and molecular mechanisms, including enhancing insulin secretion, regeneration of pancreatic β -cell, improving insulin resistance, α -glucosidase enzyme inhibitory activity and anti-inflammatory effects as well as attenuating diabetes associated oxidative stress. Suppressing hepatic glucose output and enhancing glucose uptake as key contributors in antidiabetic effect of natural remedies are mediated via stimulating glycolysis, glucose oxidation and glycogenesis, along with reducing glycogen degradation and gluconeogenesis. Since traditional natural remedies are commonly used by diabetic patients, interaction between herbs and conventional antidiabetics has also been highlighted in this study. Overall, traditional herbal remedies are possible antihyperglycemic therapeutic adjuncts and potential source of new orally active agent(s) for management of diabetes; however, more well-designed clinical trials are suggested to recognize higher levels of evidence for the confirmation of their efficacy and safety.

Key words: Diabetes, hyperglycemia, hypoglycemic effect, insulin, drug interaction, herbal medicine, medicinal plants, traditional medicine, review

INTRODUCTION

Diabetes mellitus is the most common endocrine disorder in the world. According to WHO, the prevalence of diabetes is approximately 347 million people all over the world in 2013 that will cover 5.4% of population by the year 2025. The disease is observed in all parts of the world and is quickly growing worldwide (Medagama and Bandara, 2014; American Diabetes Association, 2009). Diabetes mellitus is characterized by insulin resistance or insulin deficiency and disturbed glucose, lipid and protein metabolism. Abnormal metabolism of carbohydrates, lipids and proteins which are associated with long-term hyperglycemia, cause different metabolic disturbances, including non-enzymatic glycation of proteins, elevated generation of Reactive Oxygen Species (ROS) and peroxidation of membrane lipid (Rahimi *et al.*, 2005; Elostá *et al.*, 2012). These metabolic complications induce several pathological conditions, including a disturbance in cell function, macro and micro-vascular disorders, nephrotoxicity, retinopathy, neuropathy, dyslipidemia as well as a consequent reduction in quality of life. In addition, diabetes mellitus is considered as a major risk factor of cardiovascular diseases and an elevation in the rate of mortality (Zimmet, 1999; Pradeepa and Mohan, 2002). Although, studies to use the synthetic drugs for management of diabetes have still an important place in therapy, herbal medicine has its own place in adjunct therapy or even single therapy.

Despite diabetes was recognized by a Greek physician, Aretaeus of Cappadocia (2nd or early 3rd century) and the Persian physician Avicenna [Ibn Sina] (11th century) in his renowned medicinal book "The Canon of Medicine" (Al-Qanoon fi al-Tibb, The Laws of Medicine), this ancient disease has still remained incurable (Salimifar *et al.*, 2013). Complementary and Alternative Medicine (CAM), including acupuncture, herbal medicines, moxibustion, homeopathy, traditional medicine as well as other medicinal approaches, represents a pivotal source of investigation for the management of diabetes and its complications (Spinks *et al.*, 2014). For thousands of years, ancient civilizations and nations have used and refined a wide range of natural remedies in order to achieve efficacious remission of chronic disease. Meanwhile, numerous efficacious drugs for treating diabetes and its relevant complications in our current pharmacopoeia possess long established roots in traditional herbal medicine. Plants remain as an important source of therapeutic material for maintaining human health with unparalleled diversity and they have improved the quality of human life through disease prevention and treatment for centuries. Moreover, medicinal plants are an abundant source of biologically active molecules that play an important role in past and modern medicine, which act as a "Stepping stone" for the discovery of novel pharmacologically active ligands. This has prompted much interest in the use of traditional medicines for the treatment of diabetes (Salimifar *et al.*, 2013; Mehri *et al.*, 2011).

The current review article provides a detailed discussion summarizing the most up-to-date information and trends about

traditional herbal medicines for the management of diabetes and its complications. Thus, we comprehensively described popular medicinal plants frequently used in traditional medicine of different civilizations and cultures for the management of diabetes with focusing on recent studies confirmed their efficacy as well as their possible mechanisms of action.

MEDICINAL PLANTS TRADITIONALLY USED FOR DIABETES

The most relevant medicinal plants, used in traditional medicines of different civilizations and cultures, especially those are employed in Traditional Chinese Medicine (TCM), Traditional Iranian Medicine (TIM) and Ayurvedic medicine for the management of diabetes and its complications has been reported considering scientific name, ethnomedicinal information, preclinical and clinical investigations, cellular and molecular mechanisms of action as well as possible active constituents.

***Acacia arabica* (Leguminosae):** The fruit and gum of *A. arabica*, commonly known as acacia or thorn tree have been used for the treatment of diabetes and some metabolic syndrome from the ancient time. It has been reported that *A. arabica* has a strong antioxidant function *in vivo* in rats (Sundaram and Mitra, 2007). Three week intake of *A. Arabica* extract in streptozotocin (STZ)-induced diabetic rats resulted in significant reduction of insulin resistance and serum glucose level. It also decreased total cholesterol, triglycerides, HDL-cholesterol as well as LDL-cholesterol in diabetic rats. Antioxidant properties and reducing coenzyme Q10 (Co-Q10) seem to be responsible for its antidiabetic potential (Hegazy *et al.*, 2013). Polyphenol enriched extract from *A. meansii* bark revealed antihyperglycemic activity and reduction of body weight as well as white adipose tissue weight in mice with severe type 2 diabetes and obesity. *Acacia* polyphenols elevated energy expenditure in the liver and muscle through stimulating the expression of Carnitine Palmitoyl-Transferase1 (CPT1), acyl CoA Oxidase (ACO), Uncoupling Protein 3 (UCP3) which is mediated by activation of Peroxisome Proliferator-Activated Receptor (PPAR) α and δ . *Acacia* polyphenols have also reduced the expression of the rate-limiting enzymes of fatty acid synthesis in the liver, including Acetyl-CoA Carboxylase (ACC) and Fatty Acid Synthase (FAS) as well as PPAR- γ and lipoprotein lipase (LPL) resulted in suppression of fat accumulation and fatty liver. *Acacia* polyphenols also significantly modulated hyperinsulinemia which is mediated by elevating adiponectin secretion and lowering Tumor Necrosis Factor (TNF)- α secretion in white adipose tissue as well as enhancing the expression of glucose transporter (GLUT)-4 which is the insulin-dependent isoform of GLUTs in skeletal muscle (Ikarashi *et al.*, 2011).

The beneficial effect of *Acacia* polyphenols on insulin sensitivity and energy expenditure-related mediators in type 2

diabetes indicates its positive action in the management of diabetic metabolic syndrome. It has been suggested that the antidiabetic effect of *Acacia* bark is mainly related to polyphenolic compounds particularly robinetinidol and fisetinidol (Sundaram and Mitra, 2007; Ikarashi *et al.*, 2011).

***Boswellia carterii* and *B. serrata* (Burseraceae):** The oleo-gum resin obtained from *Boswellia carterii* and *B. serrata* trees which commonly known as Frankincense is one of the ancient drugs possesses anti-diabetic activity in traditional medicine. *Boswellia serrata* oleo-gum and its active constituents, 11-Keto- β -boswellic acid and O-acetyl-11-Keto- β -boswellic acid, demonstrated hypoglycemic activity in mice with type 1 diabetes via inhibiting pro-inflammatory cytokines associated with induction of autoimmune process in pancreatic islet including interleukin (IL)-1A, IL-1B, IL-2, IL-6, interferon (IFN)- γ , TNF- α , Granulocyte Colony Stimulating Factor (G-CSF) and Granulocyte/macrophage Colony Stimulating Factor (GM-CSF), as well as infiltration of lymphocytes into islets. Suppression of pancreatic islet tissue atrophy and apoptosis of periinsular cells mediated by anti-caspase 3 are among its main antidiabetic mechanisms (Shehata *et al.*, 2011, 2012). Rao *et al.* (2013) reported that the oleo-gum resin and the isolated compound boswellic acid improve chronic diabetic complications via suppressing polyol enzyme aldose reductase and reduction of advanced glycation endproducts *in vivo* in rat lens and rat kidney as well as *in vitro* in human recombinant cell. In addition, *B. carterii* oleo-gum resin exhibited antidiabetic potential through an increase in serum insulin, regeneration of the β -cells of Langerhans islets as well as elevating glycogenesis and reducing glycogenolysis in rats with alloxan-induced type 1 diabetes (Helal *et al.*, 2005).

***Cornus officinalis* (Cornaceae):** The fruit of *C. officinalis* commonly known as Japanese cornel dogwood has been used in traditional Chinese medicine for several therapeutic indications especially diabetes (Li *et al.*, 2004). It reduces FBS and elevated of insulin level through improving Langerhans's islet damage, number of insulin releasing β -cells and kidney glomerular function as well as blocking the mRNA expression of phosphoenolpyruvate carboxykinase (PEPCK) in STZ-induced type 1 diabetic rats (Han *et al.*, 2014; Lin *et al.*, 2011). It seems that two major active constituents from *C. Officinalis* have a pivotal role in the management of diabetes and its complications: iridoid glycosides mainly morroniside and loganin and low molecular weight polyphenols chiefly 7-O-galloyl-D-sedoheptulose. Total iridoid glycosides of *C. officinalis* reduced postprandial blood glucose level mediated by inhibition of α -glucosidase enzyme activity (He, 2011; Park *et al.*, 2011). Metabolic dysregulation associated with diabetic renal damage has been improved by iridoid glycosides and low molecular weight polyphenols elicited from *C. officinalis*. Iridoid glycosides have a

remarkable inhibitory effect on the accumulation of renal advanced glycation end-products. Likewise, low molecular weight polyphenol fractions of *C. officinalis* attenuate renal lipid peroxidation and inducible nitric oxide synthase (iNOS) (Yamabe *et al.*, 2007). Morroniside and 7-O-galloyl-D-sedoheptulose demonstrated antihyperglycemic effect via antioxidant and anti-inflammatory activity as well as protective role against diabetic nephropathy in terms of decreasing creatinine clearance, serum urea, serum glycosylated protein, serum, renal oxidative stress and improving renal sterol regulatory element binding proteins in STZ-induced diabetic rats. The anti-inflammatory mechanism of *C. officinalis* components on diabetic associated metabolic disorders of liver and kidney is mediated by inhibition of nuclear factor (NF)-B (Yokozawa *et al.*, 2008, 2010).

***Coriandrum sativum* L. (Umbelliferae):** The fruit of *C. sativum*, commonly known as coriander seed, has been used for the treatment of diabetes and its complication in TIM. Its ethanolic extract showed hypoglycemic activity in both healthy and STZ-induced type 1 diabetic rats through enhancement of activity and number of β -cells of pancreatic islet as well as insulin release from β -cells (Eidi *et al.*, 2009). An aqueous extract from the leaves and stems showed antihyperglycemic activity in normoglycemic rats through an oral sucrose tolerance test. The extract also exhibited *in vitro* α -glucosidase activity (Brindis *et al.*, 2014). Chithra and Leelamma (1999) demonstrated that the antidiabetic effect of *C. sativum* seeds are attributed to an improved utilization of glucose in liver through glycogen synthesis as well as limitation of glycogen degradation. Enhancing glycolysis and reducing gluconeogenesis are among other antidiabetic mechanisms of this fruit. The fruit aqueous extract has shown sulfonylureas-like action which is mediated via binding to sulfonylurea receptors (Gray and Flatt, 1999). In a clinical trial on 50 patients with type 2 diabetes, 6 weeks administration of capsules containing coriander seeds powder resulted in reduction of FBS, total cholesterol, triglyceride and LDL-cholesterol significantly ($p < 0.001$). Atherosclerotic index was lessened and the ratio of HDL-cholesterol/total cholesterol was improved (Parsaeyan, 2012).

***Glycyrrhiza glabra* (Fabaceae):** *Glycyrrhiza glabra*, commonly known as liquorice, is a well-known traditional herbal remedy and the root has been administrated as antidiabetic drug from ancient time (Sen *et al.*, 2011; Eu *et al.*, 2010). Glycyrrhizic acid, a triterpenoid saponin from the root, is the main bioactive component which is demonstrated antidiabetic action by improving insulin sensitivity, modulating the production of advanced glycation end products and enhancement of LPL expression in subcutaneous and visceral adipose tissues, heart and kidney. Glycyrrhizic acid also reduces plasma levels of fatty acids, LDL-cholesterol, total cholesterol, along with inhibiting lipid deposition in

type 2 diabetic rat tissues (Eu *et al.*, 2010; Cheng *et al.*, 2014). Glycyrrhizin, another main water-soluble component from the root of *G. glabra*, reduced plasma glucose level and glycosylated hemoglobin (HbA1c) and also regenerated damaged pancreas and kidney tissues in STZ-induced type 1 diabetic rats. This hypoglycemic function of glycyrrhizin is mediated by enhancement of Langerhans islet cells as well as elevating insulin secretion. Acting against diabetic associated oxidative stress through augmentation antioxidant enzyme, including superoxide dismutase (SOD) and catalase (CAT) along with suppression of lipid peroxidation, carbonyl formation and iron-mediated free radical reactions in hemoglobin are among the important antidiabetic mechanism of glycyrrhizin (Sen *et al.*, 2011).

***Morus alba* (Moraceae):** The leaves, fruits and root epidermis of *M. alba* (commonly known as mulberry) have been used in TCM for the management of several chronic disorders in particular diabetes. In folklore medicine of Asian nations, beverages containing *M. alba* leaf are consumed for improvement of body health, particularly in diabetic patients (Naowaboot *et al.*, 2009). Mulberry leaves significantly inhibit α -glucosidases, sucrase and maltase enzymes *in vitro* (Hansawasdi and Kawabata, 2006). Dietary supplementation of dried mulberry leaf powder for 5 weeks showed antihyperglycemic and reducing triglycerides and the inflammatory factor of metabolic disturbance, C-reactive protein, mediated by attenuation of insulin resistance in type 2 diabetic rats (Park *et al.*, 2009). Six weeks administration of an ethanolic extract of mulberry leaf reduced blood glucose, which was similar to the effect of insulin (4 U kg^{-1}) via suppression of lipid peroxidation. The extract also significantly reduced HbA1c in STZ-induced type 1 diabetic rats. Antiglycation and free radical scavenging activities are among its pivotal mechanisms in the management of chronic diabetes (Naowaboot *et al.*, 2009). Other antidiabetic mechanisms reported for *M. alba* leaf are glucose uptake through the activation of phosphatidylinositol 3-kinase (PI3K) signaling pathway, translocation of GLUT4 to the membrane of plasma (Naowaboot *et al.*, 2012), improvement of liver glucokinase activity and elevating serum insulin levels (Nazari *et al.*, 2013). In a randomized, double-blind, placebo-controlled trial, 12 week intake of supplementary mulberry improved postprandial glycemic control which, measured by 1,5-anhydroglucitol concentration in patients with impaired glucose metabolism (Asai *et al.*, 2011). Gallic acid, chlorogenic acid and rutin partly contribute to antidiabetic activity of mulberry leaf (Naowaboot *et al.*, 2012; Hunyadi *et al.*, 2012). Polysaccharides isolated from mulberry rhizomes perform the hypoglycemic effect in STZ-induced type 1 diabetic mice via suppressing the inflammatory response in the pancreas tissue, including TNF- α , cyclo-oxygenase-2 (COX-2), IL-8 and IL-6, along with attenuating diabetic associated oxidative stress (Guo *et al.*,

2013). The hypoglycemic potential of three isolated active compounds from root bark of mulberry including moracin M, steppogenin-4'-O-beta-D-glucoside and mulberroside A and confirmed that all of them, possess significant hypoglycemic effect in alloxan-induced diabetic mice (Zhang *et al.*, 2009).

***Phyllanthus emblica* (Phyllanthaceae):** *Phyllanthus emblica* or *Emblia officinalis*, commonly known as amla or amlaki is an important traditional medicinal fruit in Ayurveda medicine, which has been used for the treatment of a wide variety of diseases including diabetes. Experimental studies revealed that *P. emblica* exhibits several pharmacological properties including anti-inflammatory, hepatoprotective, anti-hyperlipidemic, neuroprotective, nephroprotective and cardioprotective activities (D'Souza *et al.*, 2014; Krishnaveni *et al.*, 2010). Its methanolic extract showed an antihyperglycemic effect on alloxan-induced diabetic rats. Amla fruits noticeably reduced hyperglycemia in high-fat-diet-fed/low-dose STZ-induced type 2 diabetic rats comparable to that of chlorpropamide (Daisy *et al.*, 2009; Qureshi *et al.*, 2009; Rao *et al.*, 2005). Antioxidant and free radical scavenging properties play a pivotal role in antidiabetic effect of amla fruits. The fruit suppressed the production of advanced glycation end products and TBARS mediated by enhancement of the activities of the antioxidant enzymes, SOD and CAT, along with inhibiting lipid peroxidation in STZ-induced type 2 diabetic rats (Rao *et al.*, 2005; Punithavathi *et al.*, 2011). Intake of aqueous extract of *P. emblica* fruits for 84 days demonstrated elevation of the glycogen content in the muscle cells and liver of rats with type 1 diabetes as well as decreasing glucose-6-phosphatase and glucokinase causing improvement of glycogenesis and glycolysis and attenuation of gluconeogenesis (Daisy *et al.*, 2009). *In vitro* investigation showed that the extract significantly elevates insulin sensitivity and glucose uptake into adipocytes higher than that of pioglitazone (Kalekar *et al.*, 2013). Inhibitory action on α -amylase and α -glucosidase enzymes have a pivotal role in the management of non-insulin-dependent diabetes mellitus by this fruit (Nampoothiri *et al.*, 2011). In a clinical trial on 16 patients with type 2 diabetes, 21 days intake of the fruit powder demonstrated a remarkable decrease in FBS and postprandial blood glucose concentration as well as triglycerides and total cholesterol (Akhtar *et al.*, 2011). Likewise, in a randomized, double-blind, controlled study, 12 weeks intake of *P. emblica* in 80 patients with type 2 diabetes led to improvement of diabetes associated oxidative and metabolic damage. The medicinal fruits reduced HbA1c, modulated lipid profile, suppressed oxidative stress measured by MDA, NO and glutathione (GSH) level and attenuated endothelial dysfunction based on lowering C-reactive protein which is a predictor of primary atherosclerotic damage (Usharani *et al.*, 2013). Three week administration of gallic acid, as one of the main active constituents of *P. emblica*, resulted in lessening

lipid hydroperoxides as well as reinforcement of enzymatic anti-oxidation performance, including SOD, CAT and glutathione peroxidase (GPx). Gallic acid also had a pivotal role in the neuroprotective potential of this plant in chronic diabetic animals (Prince *et al.*, 2011). Gallic acid alleviated glucolipototoxicity-associated DNA damage and apoptotic reaction which caused by high glucose concentration and regenerated pancreatic β -cell as well as stimulated the secretion of insulin mediated by insulin promoter factor 1 (Sameermahmood *et al.*, 2010). Ellagic acid, another major component of amla, revealed a protective effect toward the diabetic associated metabolic disturbance via attenuating nuclear signaling pathway of inflammatory cascades (NF-B) and enhancement of the redox sensitive transcription factors modulating redox homeostasis, nuclear factor-erythroid 2-related factor-2 (Nrf2) and carnitine palmitoyltransferase (CPT)-1 in the liver of high-carbohydrate/high-fat diet-fed type 2 diabetic rats (Panchal *et al.*, 2013).

Portulaca oleracea (Portulacaceae): The seed of *P. oleracea*, commonly known as purslane is considered as an ancient drug which has been used for the treatment of several diseases such as gastrointestinal ulceration, urinary tract infections, kidney stone and menstruation disorders in traditional and folklore medicine of different countries (Mirabzadeh *et al.*, 2013). It has been suggested that the seeds possess a pronounced antidiabetic activity in recipes of traditional medicines. Various experimental investigations have revealed positive pharmacological effects of porcelain in the management of diabetes and its metabolic complications, including hypoglycemic, hypocholesterolemic, cardioprotective and antioxidant properties (El-Sayed, 2011). Lee *et al.* (2012) demonstrated hypoglycemic activity of aqueous extract from aerial parts of *P. oleracea* in genetically-induced type 2 diabetic mice mediated by improvement of insulin secretion. The extract also alleviated diabetes-associated cardiovascular complication as well as regeneration of diabetic endothelial dysfunction through reducing triglyceride, LDL-cholesterol, vascular tension and systolic blood pressure and elevating HDL-cholesterol (Lee *et al.*, 2012). Likewise, purslane diminished diabetic vascular inflammation and leucocyte infiltration and interactions with vascular endothelial layer through inhibition of adhesion molecules, including intracellular cell adhesion molecule (ICAM)-1, endothelial vascular cell adhesion molecule (VCAM)-1, matrix metalloproteinase (MMP)-2 and E-selectin in aortic tissue (Lee *et al.*, 2012). Reinforcement of antioxidant enzymes, including GSH-R, CAT and SOD and suppression of lipid peroxidation in the kidney and liver of STZ-induced type 1 diabetic rats are among the main mechanisms of *P. oleracea* against diabetic complications (Sharma *et al.*, 2009). Studies revealed that inhibition of α -amylase and α -glucosidase enzyme activity which restrict the postprandial glucose level through delaying carbohydrate hydrolysis and absorption are

among the key contributors of the seeds in the treatment of diabetes and its complications (Ahmed *et al.*, 2013). The efficacy of purslane in diabetes has been also evaluated during two clinical trials. In a randomized double-blind placebo-controlled clinical trial on type 2 diabetic women, 8 week administration of seed powder resulted in enhancement of glucagon like peptide-1 concentrations with no significant effect on its relevant receptor (Heidarzadeh *et al.*, 2013). In another randomized double-blind placebo-controlled clinical trial, which performed on 30 patients with type 2 diabetes, 8 week administration of sachets containing purslane seeds reduced fasting and post-prandial blood glucose, serum triglycerides, total cholesterol, LDL-cholesterol, total and direct bilirubin levels as well as increased HDL-cholesterol level. Antidiabetic properties of this plant are mediated by modulation of insulin resistance and improvement of hepatic function (El-Sayed, 2011).

Punica granatum (Punicaceae): *Punica granatum* commonly called pomegranate is a large shrub or small tree with popular and delicious fruit which is native to Persia but grown and consumed all over the world. The flower of *P. granatum* is an ancient natural remedy which has been used for the treatment of several diseases including diarrhea, inflammation, peptic ulcer, hemorrhage, polymenorrhoea, aphtha, hemorrhoid, wounds and injury (Bagri *et al.*, 2009; Farzaei *et al.*, 2013b). The flower is among the main natural drugs which have been prescribed for the treatment of diabetes from a hundred years ago in TIM and Ayurvedic literatures. An aqueous extract of the flowers showed antidiabetic potential mediated by improving glucose tolerance and augmentation of antioxidant status in STZ-induced type 1 diabetic rats. It also reduced triglycerides, total LDL and VLDL-cholesterol and enhanced HDL-cholesterol in diabetic rats. Improvement of enzymatic anti-oxidative defense, including GPx, GSH-R, Glutathione S-Transferase (GST), SOD and CAT has a key role in the antidiabetic potential of Punica flower. The flower also enhanced non-enzymatic antioxidant performance mainly reduced glutathione (GSH) which protects the cellular system against the toxic effects of lipid peroxidation (Bagri *et al.*, 2009). Li *et al.* (2005) confirmed the inhibitory effect of Punica flower on α -glucosidase enzyme *in vitro* and *in vivo* and showed that this natural remedy alleviates postprandial hyperglycemia in diabetic fatty rats. A methanolic extract from the Punica flowers exhibited antidiabetic activity in glucose loading-induced hyperglycemia in Zucker diabetic fatty rats, which is considered as a genetic animal model for type 2 diabetes. This activity may be attributed to elevating insulin sensitivity and LPL activity and enhancement of GLUT4 mRNA expression which has an essential role in the maintenance of normal glucose homeostasis. Such regulatory potential of this remedy on GLUT-4 expression and insulin sensitivity was mediated by enhancement of PPAR- γ mRNA expression which is an activators of central metabolic

pathways regulating fatty acid oxidation, adipocyte differentiation and insulin sensitivity. Bio-assay guided fractionation showed that gallic acid is an active constituent responsible for improvement of insulin sensitivity as well as PPAR- γ mRNA expression (Huang *et al.*, 2005). In a clinical trial performed on 26 patients with type 2 diabetes, 8 week consumption of concentrated juice of fruits led to significant antidiabetic effect in term of reducing total cholesterol, LDL-cholesterol, LDL-cholesterol/HDL-cholesterol and total cholesterol/HDL-cholesterol (Esmailzadeh *et al.*, 2004).

Rosa spp (Rosaceae): Several species of *Rosa* is widely grown across the world for its visual beauty and scent. The flower and fruits of *Rosa* spp have claimed to possess various medicinal properties in traditional medicine of different countries particularly TIM. Antidepressant, gastric tonic, anti-ulcer and wound healing property are among the main activities attributed to this herb. The flower and fruits have a long history of safe and efficacious use in the treatment of diabetes in different countries (Farzaei *et al.*, 2013b; Gholamhoseinian *et al.*, 2009; Ninomiya *et al.*, 2007; Andersson *et al.*, 2011). The fruit is an abundant source of antioxidants, including polyphenolic components, ascorbic acid and carotenoids. Methanolic extract from *R. damascena* flowers demonstrated dose-dependent hypoglycemic effect on maltose loading-induced plasma glucose peak in normal and STZ-induced diabetic rats, which are executed by noncompetitive inhibition of α -glucosidase enzyme. The α -glucosidase inhibitory and hypoglycemic effect of the flower was comparable to the conventional drug, acarbose (Gholamhoseinian *et al.*, 2009). *Rosa rugosa* significantly improved body weight gain and kidney and liver function in STZ-induced type 1 diabetic rats. Likewise, this plant reduced blood glucose and glycosylated protein levels, indicating regulation of glucose metabolism. Disturbance in glucose metabolism and accumulation of glycosylated protein leads to oxidative stress, which was diminished by *R. rugosa* extract (Cho *et al.*, 2004). The fruits of *R. canina*, commonly known as rose hip, which is consumed as a strong antidiabetic natural drug in folklore medicine of different countries especially Iran and Turkey, exhibited the hypoglycemic effect in type 1 diabetic rats. Reinforcement of antioxidant function and scavenging free radicals are among the main contributors in the antidiabetic potential of rose hip (Orhan *et al.*, 2009). Rose hip and is active constituent, trans-tiliroside, significantly ameliorated glucose tolerance and insulin resistance associated obesity in mice with diet-induced obesity (Ninomiya *et al.*, 2007; Andersson *et al.*, 2011). In a randomized, double-blind, crossover clinical trial, metabolic potential of daily intake of *R. canina* powder drink was evaluated in 31 obese patients with normal or impaired glucose tolerance. After 6 week, total plasma cholesterol, LDL-cholesterol, LDL/HDL ratio, systolic blood pressure, as well as the Reynolds risk assessment score

for cardiovascular disease significantly decreased compared to that of control group (Andersson *et al.*, 2012).

Vitis vinifera (Vitaceae): *Vitis vinifera* commonly known as grape is an important medicinal plant which has been used traditionally for the treatment of different ailments across the world. The leaf, unripe fruits as well as ripe fruits are considered as a wound healer, hematopoietic, anti-ulcer natural drug in traditional herbal medicine (Farzaei *et al.*, 2013a; Hwang *et al.*, 2009; Pinent *et al.*, 2004). The unripe fruits possess antidiabetic action in TIM. Crude extract of grape seed and the ethylacetate/ethanol fraction demonstrated antidiabetic effect in term of reducing FBS and HbA1c in mice with genetically induced type 2 diabetes (Hwang *et al.*, 2009).

One of the main roles of an efficacious antidiabetic drug is acting as insulinomimetic agent and modulating the impaired action of insulin characterized by insulin resistance. The procyanidins derived from seeds perform an antihyperglycemic activity in STZ-induced type 1 diabetic rats. This antihyperglycemic effect was boosted by coadministration with a low dose of insulin to such an extent that was comparable to the standard antidiabetic drugs, metformin and troglitazone, indicating the insulinomimetic potential of the procyanidins. Pinent *et al.* (2004) demonstrated that the insulinomimetic potential of grape seeds procyanidins is mediated by upgrading glucose uptake in insulin sensitive cells and stimulation of insulin pathway mediators, including PI3K, P38-Mitogen-Activated Protein Kinases (MAPK) and GLUT4 (Pinent *et al.*, 2004). Jin *et al* reported that the oligomeric proanthocyanidins derived from grape seeds protect nerve fiber against diabetic peripheral neuropathy and oxidative damage in high-fat diet-induced type 2 diabetic mice (Jin *et al.*, 2013). Proanthocyanidin-rich extract of grape seeds showed antidiabetic potential, including reducing advanced glycation end products, HbA1c and FBS, along with reduction of kidneys/body weight ratio, BUN, creatinine, glomerular hypertrophy and interstitial fibrosis, indicating therapeutic activity in rats with diabetic nephropathy induced by STZ. Suppressing overexpression of oxidative stress proteins, i.e., glutathione-S-transferase Mu (GSTM), glutamate carboxypeptidase and beta actin protein are among its pharmacological mechanism in diabetic nephropathy (Li *et al.*, 2008).

The efficacy of *V. vinifera* fruits have been evaluated in different clinical studies. In a randomized double-blind placebo controlled clinical trial on 38 patients with first-degree relatives of type 2 diabetes, 9 weeks consumption of polyphenol extract of the fruits resulted in significant improvement of hepatic insulin sensitivity index and cellular insulin tolerance (decreasing glucose infusion rate), mediated by alleviating diabetic oxidative stress in terms of suppressing systemic and muscular malondialdehyde (MDA) level, protein carbonylation as well as mitochondrial respiration

(Hokayem *et al.*, 2013). However, in another randomized double-blind placebo controlled clinical trial performed by Pourghassem-Gargari *et al.* (2011), daily intake of capsules containing grape seed ethanolic extract for 2 months modulates Total Antioxidant Capacity (TAC) and SOD, with no significant effect on FBS, GPx and MDA levels (Pourghassem-Gargari *et al.*, 2011).

Resveratrol, one of the main antioxidant constituents in grape, possesses protective effect against chronic inflammatory diseases, cardiovascular disease and diabetes in wide variety of experimental studies (Brasnyo *et al.*, 2011; Farzaei *et al.*, 2015). One clinical trial evaluated the therapeutic potential of daily intake of resveratrol in type 2 diabetic patients. Four weeks administration of this grape derived polyphenol demonstrated significant antidiabetic effect through improvement of insulin sensitivity index (homeostasis model of evaluation for insulin resistance) as well as reducing urinary ortho-tyrosine excretion as a marker of oxidative stress, indicating its protective role against diabetic oxidative damage. Likewise, resveratrol enhances phosphorylation of protein kinase B (Akt) in platelets, which has an essential contributor in insulin signaling pathway. While the polyphenol has no significant effect on β -cell function and serum insulin level (Brasnyo *et al.*, 2011).

***Withania somnifera* and *W. coagulans* (Solanaceae):** The fruits are important medicinal plant in Ayurvedic system of medicine in India and considered as an official drug in Indian Pharmacopoeia. The fruits have received considerable attention for their therapeutic benefit in chronic degenerative diseases. The fruits have been claimed to possess various pharmacological properties containing immunomodulating, anti-inflammatory, antihyperglycemic, hypolipidemic, antitumor, antistress and wound healing activities (Ojha *et al.*, 2014). Aqueous extract of *W. coagulans* fruits showed significant reduction in FBS as well as serum cholesterol in STZ-induced diabetic rats (Hemalatha *et al.*, 2004). Likewise, *W. coagulans* demonstrated hypoglycemic effect and modulating glucose tolerance test in normal, mild, moderate and severe diabetic rats (Jaiswal *et al.*, 2009). Five week administration of aqueous extract from *W. somnifera* significantly attenuates hyperglycemia, hyperinsulinemia and accumulation of glycosylated hemoglobin, as well as prevention of the rise of homeostasis model assessment of insulin resistance in rats with non-insulin-dependent diabetes mellitus (Anwer *et al.*, 2008). Enhancement of liver and muscle glycogen as well as improvement of enzymes involved in glucose homeostasis, including glucokinase, phosphofructokinase and glucose-6-phosphatase are among the main antidiabetic mechanisms of *W. coagulans* in preclinical study of STZ/nicotinamide-induced diabetes (Shukla *et al.*, 2012a). The dietary supplement of phenolic compounds from *W. somnifera* extract showed antidiabetic properties mediated by an improvement of liver glycogen, along with the elevating plasma level of the antioxidants vitamin C and E as well as

GPx, SOD, CAT, GST and GSH in liver, heart and kidney in alloxan-induced diabetic rats (Udayakumar *et al.*, 2010). *Withania coagulans* fruits also exhibited significant regulation in serum lipid profile as well as tissue lipid content mediated by modulating HMG-CoA reductase as well as ACC enzyme activity, indicating its therapeutic potential on diabetic dyslipidemia in rats with STZ/nicotinamide-induced diabetes (Shukla *et al.*, 2012b). In a clinical trial on 53 patients with type 2 diabetes mellitus, 3 months intake of *W. coagulans* fruits powder, lead to attenuation of polyphagia, polyuria, joint pain, weakness, burning and tingling sensation. Moreover, significant reduction of FBS, postprandial blood glucose, cholesterol and triglyceride was recorded in biochemical analysis (Upadhyay and Gupta, 2011).

INTERACTION BETWEEN TRADITIONAL HERBS AND CONVENTIONAL ANTIDIABETIC MEDICATIONS

Because of lack of desired efficacy of conventional pharmaceutical agents for management of diabetes mellitus as well their adverse events and high cost, a wide range of patients suffering from this disease prefer to use Complementary and Alternative Medicines (CAMs) especially herbal medicines. The prevalence of CAMs usage among patients with diabetes is different in various regions: From 17% in England to 80% in Africa (Leese *et al.*, 1997; Chang *et al.*, 2007). More than 400 medicinal plants have been recorded as therapeutically beneficial in the management of diabetes and its complications (Chang *et al.*, 2007; Modak *et al.*, 2007). Since herbal remedies are commonly used by diabetic patients, understanding the interaction between herbs and conventional antidiabetics is highly important. Regarding multiple prescribed pharmacotherapy, patients with diabetes mellitus are considered as a high-risk group for herb-drug interactions potential, causing noticeable morbidity from inadvertent alterations in blood glucose level (Bush *et al.*, 2007). A list of medicinal plants that exhibited potential interactions with conventional anti-diabetic drugs have been shown in Table 1. Herbal medicines with potential of induction of hypoglycemia, including *Panax ginseng*, *Trigonella foenum-graecum*, *Momordica charantia*, *Arctium lappa*, *Allium sativum*, *Gymnema sylvestre* and *Plantago Psyllium* seeds have interaction with specific antidiabetic drugs because of enhancing the probability of hypoglycemia (Kuhn, 2002). There are several evidences reporting hypoglycemia with concomitant intake of *Momordica charantia* and *Allium sativum* with chlorpropamide (Aslam and Stockley, 1979). *Ginkgo biloba* can enhance the hepatic metabolic clearance rate of insulin as well as some antidiabetic drugs causing impaired insulin-mediated glucose metabolism and increase FBS. In a preclinical study ginkgo extract showed elevation of cytochrome P2C9 (CYP2C9) activity, a main CYP isoenzyme metabolizing tolbutamide and resulted in reducing the hypoglycemic effect of this drug in

Table 1: Important herbs that might show interactions with conventional antidiabetic agents

Plants	Drug	Mechanism of interaction	References
<i>Aloe vera</i>	Glibenclamide	Pharmacodynamics (↓ likelihood of hypoglycemia)	Bunyaphatsara <i>et al.</i> (1996)
<i>Opuntia streptacantha</i>	Antidiabetic drugs including glyburide, metformin, rosiglitazone and acarbose	Pharmacodynamics (↓ likelihood of hypoglycemia)	Frati-Munari <i>et al.</i> (1989), Meckes-Lozyoa and Roman-Ramos (1986)
<i>Citrus fruits</i>	Pioglitazone and nateglinide	Pharmacokinetic (↓ CYP3A activity: ↑ pioglitazone and nateglinide level)	Fujita <i>et al.</i> (2003)
<i>Panax ginseng</i>	Antidiabetic drugs particularly sulfonylureas	Pharmacodynamics (↓ likelihood of hypoglycemia)	Kuhn (2002)
<i>Gymnema sylvestre</i>	Antidiabetic drugs particularly sulfonylureas	Pharmacodynamics (↓ likelihood of hypoglycemia)	Kuhn (2002)
<i>Arctium lappa</i>	Antidiabetic drugs particularly sulfonylureas	Pharmacodynamics (↓ likelihood of hypoglycemia)	Kuhn (2002)
<i>Trigonella foenum-graecum</i>	Antidiabetic drugs particularly sulfonylureas	Pharmacodynamics (↓ likelihood of hypoglycemia)	Kuhn (2002)
<i>Plantago psyllium</i>	Antidiabetic drugs particularly sulfonylureas	Pharmacodynamics (↓ likelihood of hypoglycemia)	Kuhn (2002)
<i>Allium sativum</i>	Antidiabetic drugs particularly sulfonylureas	Pharmacodynamics (↓ likelihood of hypoglycemia)	Kuhn (2002) and Aslam and Stockley (1979)
<i>Momordica charantia</i>	Antidiabetic drugs particularly sulfonylureas	Pharmacodynamics (↓ likelihood of hypoglycemia)	Kuhn (2002) and Aslam and Stockley (1979)
<i>Glycyrrhiza glabra</i>	Tolbutamide	Pharmacokinetic (↓ intragastric pH, ↓ gastric emptying rate: ↓ tolbutamide level)	Nishimura <i>et al.</i> (1998)
<i>Ginkgo biloba</i>	Tolbutamide	Pharmacokinetic (↓ CYP2C9 activity: ↓ tolbutamide level)	Sugiyama <i>et al.</i> (2004)
Quercetin enriched plant extracts	Pioglitazone and nateglinide	Pharmacokinetic (↓ CYP3A activity: ↑ pioglitazone and nateglinide level)	Umathe <i>et al.</i> (2008)

diabetic patients (Kudolo, 2001; Sugiyama *et al.*, 2004). *Glycyrrhiza glabra* extract reduced plasma level of tolbutamide mediated by increasing intragastric pH and suppressing gastric emptying rate (Nishimura *et al.*, 1998). *Opuntia streptacantha* caused hypoglycemia when administered with antidiabetic drugs, including glyburide and metformin, rosiglitazone and acarbose (Frati-Munari *et al.*, 1989; Meckes-Lozyoa and Roman-Ramos, 1986). *Aloe vera* juice showed hypoglycemic effect while administered along with glibenclamide in patients with diabetes mellitus (Bunyaphatsara *et al.*, 1996). Quercetin as a most abundant dietary flavonoid present in a wide variety of vegetables, fruits and beverages can reduce the metabolism of pioglitazone and elevate its bioavailability via suppressing the CYP3A, a class of CYP450 isoenzymes metabolizing pioglitazone and nateglinide (Umathe *et al.*, 2008). Some other medicinal plants with specific effects on hepatic metabolizing enzymes are also proposed to interact with novel antidiabetic agents, but clinical and preclinical studies have not performed in order to evaluate their herb/drug interactions (Pal and Mitra, 2006). As an example, citrus fruits can inhibit CYP3A and elevate the bioavailability of pioglitazone and nateglinide (Fujita *et al.*, 2003).

Diabetes mellitus is a common metabolic disorder in the endocrine system. The prevalence and incidence of diabetes mellitus is increasing dramatically across the world (Shaw *et al.*, 2010; Hosseini and Abdollahi, 2012; Hasani-Ranjbar *et al.*, 2013). This chronic metabolic disease

possesses a widespread impact on the quality of life, health parameters and life expectancy of patients, along with the important problems in the health care system. The disease is a metabolic disorder characterized by hyperglycemia, abnormal lipid and protein metabolism, which in the long term leads to severe complications affecting the retina, kidney, liver and nervous system that are more fatal than the primary disease, leading to increased morbidity (Nathan *et al.*, 1997; Safavi *et al.*, 2013).

Earlier the discovery of insulin in 1920 and even during the progress of oral antihyperglycemic drugs, the main therapeutic approaches of diabetes mellitus and its complications involved dietary manipulation, starvation and the intake of various medicinal plants or their extracts based on the traditional and folklore medicines (Akhtar and Ali, 1984; Bailey and Day, 1989). Traditional medicines, all over the world suggest a wide range of remedies for the management of chronic disorders as in diabetes mellitus. Traditional therapy of diabetes mellitus aims not only to attain a euglycemic condition, but also to treat the roots which the disease results from. Medicinal plants and plant-derived natural agents are among the most important resources of traditional medicines. Over the last few decades, research tendency toward discovery of bioactive components from plant extracts as models for designing novel medicines has been grown up. Traditional herbal medicines are widely available, highly tolerable, much less expensive and having mostly less side effects as compared to synthetic prescription drugs

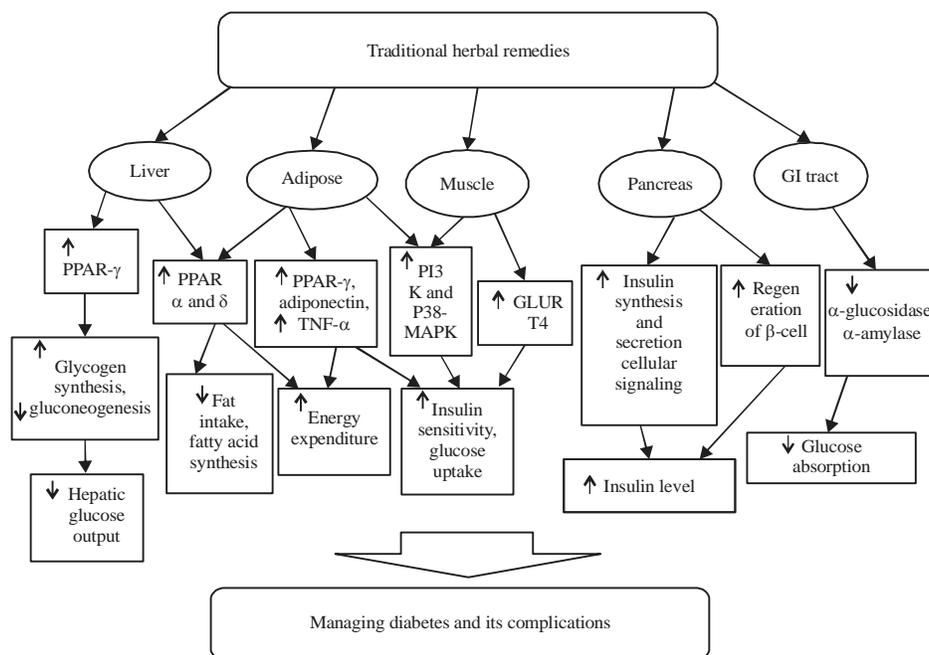


Fig. 1: Molecular and cellular mechanisms for the efficacy of traditional herbal remedies and their phytochemicals in diabetes mellitus and its relevant complications

(Farzaei *et al.*, 2013a; Bahramsoltani *et al.*, 2014; Rahimi *et al.*, 2010). A large body of scientific evidences suggests that traditional herbal medicines may possess therapeutically beneficial in the management of diabetes and its complications. Since diabetes mellitus is a complex metabolic disease, multiple cellular and molecular mechanisms of action must be present in a medicinal plant to be potential for management of this disease. Figure 1 presents the molecular and cellular mechanisms demonstrated for the efficacy of traditional herbal remedies and their phytochemicals in diabetes mellitus and its relevant complications. Various *in vitro* and *in vivo* research studies support the efficacy of these traditional natural medicaments. However, the randomized clinical trials in this area are scarce.

Given the high prevalence of intake of herbal medicine among patients with diabetes mellitus, interactions between these herbs and conventional antidiabetic agents should be considered. Herbal medicines with potential of induction of hypoglycemia possess interaction with chemical antidiabetic drugs due to raising the probability of hypoglycemia. Stimulating or inhibiting the CYP isoenzymes which metabolizing antidiabetic drugs, including CYP2C8, CYP2C9, CYP2C19 and CYP3A4 are considered as the main reason of herb/drug interactions. Pharmacokinetic herb/drug interactions can result in whether elevating drug metabolism and lowering the bioavailability and efficacy of such drugs or reducing drug metabolism and enhancing adverse events antidiabetic agents.

CONCLUSION

It can be concluded that traditional herbal remedies are possible anti-hyperglycemic therapeutic adjuncts and potential source of new orally active agent(s) for diabetes treatment. Further, well-designed randomized clinical trials are suggested in order to recognize higher levels of evidence for the confirmation of traditional herbal medicines efficacy and safety in the management of diabetes and its complications.

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