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Anti-Diabetic potential of herbal remedies on the glucose transport gene (GLUT) in liver and skeletal muscles

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ABSTRACT:

For a long time, several herbal medicines have been used for the treatment of diabetes in the form of compound drugs. Moreover, after the references made by researchers on diabetes mellitus, investigations on the hypoglycemic activity of compound drugs from medicinal plants have been more important. Although, the molecular mechanisms behind this effect is not much explored yet. There are various approaches to reduce the diabetes effect and its secondary complications, and herbal drugs are more preferred due to its less side effects and low cost. One of the major factors in the development of diabetes and its complications is the damage induced by free radicals. Therefore antidiabetic compounds with antioxidant properties would be more beneficial. It is hypothesized that the insulin mimetic effect, hypoglycemic effect and β-cell function of herbal remedies might add to glucose uptake through improvement in the expression of genes of the glucose transporter (GLUT) family in liver and skeletal muscles. Here we selected some plants with the ability to control blood glucose as well as to modulate some of the mechanisms involved in insulin resistance like β-cell function, glucose transport (GLUT) gene and incretin related pathways. Therefore, plants remedies may be appealing as an alternative and adjunctive treatment for diabetes mellitus.

Keywords:
Herbal Remedies, Glucose Transporter (GLUT), mRNA.

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INTRODUCTION

Through ages people have utilized natural resources especially plants to maintain good health and fighting against infections, pain and diseases. In the past 200 years we have seen an increased extinction of plant species due to industrialization and a decline in knowledge of traditional medicinal which relies heavily on plants. World Health Organization (WHO) identifies 21,000 plant species with medicinal value from different parts of the world. Though, traditional medicine has been replaced by modern medicine almost everywhere, we are becoming increasingly aware of its many shortcomings, and chief among them are its ineffectiveness against many conditions and diseases, harmful side effects and increasing cost of treatment. The present review is an attempt to discuss the role of herbal drugs preparations and plants used in the treatment of diabetes and effect of herbal drug on the Glucose Transporters (GLUTs) genes. All eukaryotic cells rely chiefly on glucose for energy production which is transported across the membrane via Glucose transporters. GLUTs are expressed in all cell types in humans where they are primarily responsible for sugar uptake destined for metabolic pathways (Augustin, 2010; Thorens and Mueckler, 2010).

Diabetes and significance

Among lifestyle diseases diabetes mellitus is emerging as a life threatening condition right behind cancer and cardiovascular disease. It is a chronic metabolic disease with high prevalence, morbidity and mortality rate (Kannel *et al*., 1979; King *et al*., 1998). Diabetes mellitus doesn’t have any geographical specificity with nearly 4% of world’s population affected by this deadly disease and the death toll is likely to increase by 5.4% in the year 2025 (Kim *et al*., 2006). Additionally diabetes is known to be a risk factor for other diseases as well. The International Diabetes Federation (IDF) estimates that 285 million people, 6.4% of the world population, suffered from diabetes in 2010 and this prevalence will increase to 439 million people, 7.7% of the world population by the year 2030 (Shaw *et al*., 2010). Over 90% of patients are diagnosed with type 2 diabetes mellitus (T2DM) (Boyle *et al*., 1999; Attele *et al*., 2002). The cost of health care associated in diabetes continues to grow and becoming a big economic burden for diabetic patients and countries. Nearly US$ 174 billion were spent in the year 2007 alone in the United States treating 17.5 million adults (Cashen *et al*., 2008).

It is a complex metabolic disorder resulting due to the lack of insulin or inability of cells to respond to insulin. Insulin insufficiency due to the lack of functional beta cells results in type 1 diabetes mellitus (T1DM, insulin dependent) while patients with T2DM (insulin dependent) are unable to respond despite producing normal amounts of insulin. Patients with type 1 insulin are totally dependent on external sources of Insulin however, patients with type 2 insulin can be managed with dietary changes, medications and exercise. Nearly 90% of cases are of T2DM and it is the most common form of diabetes. General symptoms of diabetes includes: high levels of sugar in the blood, unusual thirst, frequent urination, extreme hunger and loss of weight, blurred vision, nausea, vomiting, tiredness, extreme weakness, irritability, and mood changes.

Pathophysiology of diabetes

A complete pathophysiological profile of diabetes remains to be ascertained, however, mounting evidence points towards the crucial role of free radicals in the pathogenesis and development of diabetic complications. (Oberlay *et al*., 1988; Baynes *et al*., 1997; Lipinski *et al*., 2001). T1DM is a catabolic disorder in which circulating insulin is very low or absent, plasma glucagon is elevated, and the pancreatic β-cell fail to respond to all insulin secretory stimuli.

Free radicals are extremely reactive species produced as a byproduct of cellular metabolism and damages cellular molecules like nucleic acid, proteins and lipids leading to altered cellular function. Many studies show the role of antioxidants that could neutralize free radicals, in reducing the effects of aging and cancer (Kubish *et al*., 1997; Naziroglu *et al*., 2001). These antioxidants also have the ability to prevent experimentally induced diabetes in mouse models and reduce diabetic complications. (Lipinski *et al*., 2001). Mounting evidence from epidemiological studies suggests that genetic and environmental factors are most common causes for diabetes. Both factors contribute to become insulin resistance and loss of β-cell function that result in impairment in insulin action, insulin production, or both.

Nearly 5% of western population is affected by T2DM that is the most common endocrine disorder (Zimmet *et al*., 2001; Shaw *et al*., 2010; Centers for Disease Control and Prevention, US, 2011). Insulin is a very important protein hormone that regulates the metabolism of fat, glucose and protein in cells. Patients with T2DM suffer from both reduced insulin secretion and inability to respond to insulin (Naziroglu *et al*., 2001). Insulin resistance has been attributed to elevated levels of free fatty acids in plasma, (Zimmet *et al*., 2001) leads to decreased glucose transport into muscle cells, elevated, increased breakdown of fat and hepatic glucose production. Insulin is solely produced by pancreatic beta cells and any defects in its production or mode of action results in grave metabolic consequences. Increased cardiovascular risk starts to appear much before the development of hyperglycemia. Targeting beta cells early in the disease progression has resulted in a new approach to treat T2DM. (Boden *et al*., 1996). During the induction of insulin resistance, such as is seen after steroid administration, high-calorie diet, or physical inactivity, increased glucagon levels and increased Glucose-dependent Insulinotropic Polypeptide (GIP) levels accompany glucose intolerance; however, postprandial Glucagonlike Peptide-1 (GLP-1) response is unaltered (Tourrel *et al*., 2001). Several growth factors, cell cycle mediators and nuclear factors regulate beta cell homeostasis and maintaining and enhancing beta cells function has the ability to stabilize and reverse the detrimental effect of T2DM (Leahy *et al*., 2010; Ackermann *et al*., 2007).

Role of glucose transport gene (glut)

Glucose is transported across the cell membrane by a family of integral membrane protein GLUT proteins that catalyzes facilitated diffusion of pentose and hexose sugar molecules down a concentration gradient. GLUT protein contains 500 amino acids and share 25-68% sequence identity with one another (Thorens and Mueckler, 2010). Nearly all the mammalian cells express GLUTs and some of them help in the transport of dehydroascorbate, urate or myoinositol apart from glucose. Most cells express one isoform of GLUTs that helps in the transport of major monosaccharide unit while other 13 isoforms are expressed at a lower level. Inhibition of GLUT-1-mediated sugar transport in human red cells by specific inhibitors reduces glucose permeability by five orders of magnitude (Naftalin *et al*., 1977). The GLUTs, therefore, provide a pathway for cellular sugar import across the cell membrane which is otherwise a very effective barrier to trans-membrane flow of monosaccharaides. In most cells it is the glucose import which is the most important function because it is a source of metabolic fuel, however, in some cells (liver, kidney and gastrointestinal tissues) export is required.

The major family of glucose transporters is the GLUT gene family. The principal insulin-sensitive glucose transporter in the liver and muscle is insulin-sensitive glucose transport gene (GLUT). Among the large super family of transport facilitators GLUT genes form a subset and includes 12 SLC2A genes numbered 1 -12 encoding 12 GLUT proteins. GLUT1 is expressed highly in erythrocytes and brain and GLUT2 is associated with Fanconi-Bickel syndrome. GLUT3 is responsible for glucose transport across neuronal plasma membrane. Insulin regulated glucose transport in adipose tissues, heart muscles and skeletal muscles are carried out by GLUT4. Skeletal muscles that are primary site for dietary glucose disposal, metabolizes glucose via glycolysis and glycogen synthesis (Ikemoto *et al*., 1995). GLUT4 regulation is also involved in obesity-induced insulin resistance characterize by increased blood glucose and plasma insulin levels. GLUT4 mRNA and protein expression are reduced during adipose tissue expansion which is another major site for dietary glucose disposal and might represent an adaptive response in order to prevent brain against hypoglycemia (Garvey *et al*., 1991; Fronzo *et al*., 1985). GLUT5 is highly expressed in intestine, testis, kidney, and GLUT7 expression is currently unknown. GLUT5 and GLUT7 are present contiguously on chromosome 1p36.2 with a high degree of sequence similarity (58% identical amino acids). GLUT5 is expressed in brain microglia though its function remains unclear (Kern *et al*., 1990; Slentz *et al*., 1992). Many studies indicate that glucose transport response to insulin in liver and skeletal muscle is heavily influenced by GLUTs. In fact one of the major reasons of hyperglycemia is the decrease in glucose transport gene levels. Glucose unresponsiveness with GLUT gene impairment is a hallmark of T2DM and restoring GLUT levels would enhance uptake of glucose in liver and help combat hyperglycemia (Thorens *et al*., 1992).

Herbal therapy for diabetes

Throughout the human history people have relied on natural products, particularly on plants. Medicinal plants were applied to treat a wide range of disease categories (Basch *et al.,* 2003) and maintain good health. Past 200 years have witnessed not only an acceleration in the rate of extinction of plant species but also in erosion of traditional knowledge related to the medicinal properties and uses of herbal plants. Although herbal medicine systems are sometimes misinterpreted as being unscientific and anachronistic but their long-term existence proved that they are able to compete with modern medicine at some level. Therefore, use of medicinal plants, mainly to distinguish the ancient and culture-bound health care practices, which existed before the application of science to health care in official modern scientific medicine or allopathic. An anti-diabetic herb with many phytochemicals may have multiple benefits by targeting several metabolic pathways. One study demonstrated that a combination therapy of modern medicine and herbal medicine exhibited a better (synergistic) effect than either medicine alone (Kaur *et al*., 2012). Therefore, herbal medicines can be a complement of modern therapy in T2DM and provide hope for a cure. In our pervious study we observed antidiabetic effect of *catharanthus roseus* on STZ induced diabetes and comparison with Metformin, treatment with *c. roseus* in diabetic wistar rats, the contents of glucose transport gene mRNA were restored to near normal values (Waleed *et al*., 2015).

All traditional medicines have their roots in medicinal values and household remedies and play a prominent role in human health care. WHO has listed 20,000 medicinal plants used in different parts of the world, and among them, 1200 plants have been claimed to be anti-diabetes remedies (Marles and Farnsworth 1995; Habeck 2003). Over 400 plants and 700 recipes compounds have been scientifically evaluated for T2DM treatment (Singh *et al*. 2011). Metformin was developed based on a biguanide compound from anti-diabetic herbs, French lilac, and is now a first line drug for T2DM (Oubre *et al*., 1997).

Selected medicinal herbs for diabetes

More than 400 herbals and their compounds have shown anti-diabetic activities. Instead of listing 400 herbals and their compounds, here, we selected some plants with the ability to control blood glucose as well as to modulate some of the mechanisms involved in insulin resistance like β-cell function, glucose transport (GLUT) gene and incretinrelated pathways.

Acacia arabica

Acacia arabica is a popular ornamental and medicinal tree. Use of *A. arabica* for the prevention and treatment of various health ailments has been in practice for hundreds of years. The plant extract acts as an anti-diabetic agent by acting as secretagouge to release insulin. It contains chiefly arabin which is the mixture of calcium, magnesium and potassium salts of arabic acid. It induces hypoglycemia in control rats but not in alloxanized animals. Powder of *Acacia arabica*, when administered (2, 3 and 4 g/kg body weight) to normal rabbits, induced a hypoglycemic effect by initiating the release of insulin from pancreatic β-cell (Wadood *et al*., 1989).

Aegle marmelos

Aegle marmelos leaves (family of Rutaceae), which is also called as *61/va* in ancient Sanskrit, has been used as herbal drug in the Indian subcontinent for over 5000 years. The hepatoprotective effect of *A. marmelos* in al-cohol-induced liver injury was evaluated for biochemical parameters. Many studies have validated the ethnomedicinal uses and indicated that the fruit possesses broad range of therapeutic effects like antioxidant, inhibition of lipid peroxidation, antibacterial, antiviral, gastroprotective, anti-diarrheal, hepatoprotective and anti-diabetic effects. The aqueous extract of leaves of *A. marmelos* has reported to improves digestion and reduces blood sugar and urea, serum cholesterol in alloxanized rats. Instead of exhibiting hypoglycemic activity, the extract also prevented blood sugar level at 1h in oral glucose tolerance test (Karunanayake *et al*., 1984).

Allium cepa

Allium species are among the oldest cultivated crops. Diverse representations in Egyptian artifacts dating to 2700 BC suggested that onions had been cultivated and in wide use by that time. Many ether soluble fractions and insoluble fractions of dried *Allium* powder show anti-hyperglycemic activity in the diabetic rabbits. *Allium cepa* is also known to have antioxidant and hypolipidaemic activity. Sulfur containing amino acid from *Allium cepa*, S-methyl cysteine sulphoxide induced diabetic rats significantly controlled blood glucose and lipids in serum and normalized the activities of liver hexokinase and glucose 6-phosphatase (Roman *et al*., 1995; Kumari *et al*., 1995). Scientific and pharmacological studies have found evidence that *Allium cepa* or their derived compounds have antimicrobial and antifungal properties, and may also be of benefit in preventing or treating heart disease and diabetes.

Allium sativum

Allium sativum is a strongly aromatic crop plant that has been cultivated for thousands of years, belonging to the liliaceace. It has been used as a medicinal agent for thousands of years and is renowned throughout the world for its distinctive flavor and health-giving properties. *Allium sativum* contains phosphorus, iron and copper, which have multiple beneficial effects like antimicrobial, antithrombotic, hypolipidemic, anti-arthritic, antitumor and anti-diabetic effects (Sheela *et al*., 1992). It also contains allyl propyl disulphide, diallyl disulphide and alliin, which increase hepatic metabolism and insulin release from pancreatic β-cell and/or insulin sparing effect (Bever *et al*., 1979).

Active compound allyl propyl and diallyl sulfide have played a role in decrease blood glucose levels. The aqueous homogenate orally administered to rabbits significantly increased hepatic glycogen, free amino acid content, decreased fasting blood glucose, and triglyceride levels in serum (Zacharias *et al*., 1980).

Aloe vera* and *Aloe barbadensis

Aloe vera belong to *Aloaceae* family, has been used for medicinal purpose from a very long time. Many studies worldwide indicated that aloe is a general tonic for the immune system and helps in fighting of all kind illness. Aloe has an important role to play in managing diabetes. Some studies have found that two tablespoons of aloe decreased blood sugar levels. Extracts of aloe effectively increased glucose tolerance in normal and diabetic rats (Shibib *et al*., 1993). *Aloe vera* reduced hyperglycemia and hypercholesterolemia in diabetic patients. Active compound of *Aloe vera,* aloeres in which inhibits α-glucosidase activity and intestinal glucose absorption. Single and chronic doses of *Aloe vera* showed hypoglycemic effect in diabetic rats. *Aloe vera* showed stimulation of synthesis and/or release of insulin from pancreatic β-cell (Vats *et al*., 2002). *Aloe vera* and its active compound suppressed the activity of α-glucosidase (gut glucose absorption) and insulin resistance. *Aloe vera* also has an anti-inflammatory activity and improved wound healing in diabetic mice (Rai *et al.,* 1997).

Azadirachta indica

Azadirachta indica belongs to Meliaceae family contains glycerides of saturated and unseturated fatty acid. The main fatty acids are oleic and stearic acids and 2% are sulpher containing compounds like nimbidin, nimbin, nimbinin, nimbidol. Hydroalcoholic extracts of *A. indica* showed antihyperglycemic activity in diabetic rats and this effect is due to increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm (Chattopadhyay *et al*., 1987). Apart from having anti-diabetic activity, *A. indica* also has anti-bacterial, ant-imalarial, anti-fertility, hepatoprotective and antioxidant activities (Biswas *et al*., 2002). Leaves extract of *A. indica* may be helpful in controlling the development of hyperlipidemia and atherosclerosis in diabetic subjects in view of its antihyperlipidemic activity. *A. indica* has been used extensively by humankind to treat various ailments since prehistoric times.

Caesalpinia bonducella

Caesalpinia bonducella is widely distributed throughout the coastal region of India and widely used for controlling blood sugar by the tribal people of India. *C. bonducella* has been used in different system of traditional medication for the treatment of diseases. *C. bonducella* contained various alkaloids, glycosides, terpenoids and saponins. *C. bonducella* has been reported as anti-diabetic, anti-asthmatic, anti-bacterial, anti-inflammatory, anti-oxidant, hypoglycemic, anti-tumor and immunomodulatory. Aqueous and ethanolic extracts showed potent hypoglycemic activity in chronic T2DM models and also increased glycogenesis thereby increasing liver glycogen content (Chakrabarti *et al*., 2003). Aqueous and ethanolic (50% each) extracts of *C. bonducella* seeds showed antihyperglycemic and hypolipidemic activities in diabetic rats (Sharma *et al*., 1997). The antihyperglycemic action of the extracted seed is due to the blocking of glucose absorption. *C. bonducella* has the potential to act as anti-diabetic and anti-hyperlipidemic (Kannur *et al*., 2012).

Coccinia indica

Coccinia indica, an herb grows abundantly in India, has been used in traditional treatment of diabetes. *C. indica* is also known by the scientific names *Coccinia indica* and *Coccinia cordifolia*. *C. indica* has been used as an anti-diabetic drug in Ayurveda since ancient times and also used as a vegetable. Leaves of *C. cordifolia* have a potential hypoglycemic agent in healthy individuals thus it has been used for the treatment of patients with mild diabetes independent of energy/food intake or weight loss. An aqueous alcoholic extract of *C. cordifolia*, has been reported on the blood glucose levels of newly detected T2DM patients requiring only dietary or lifestyle treatment (Kamble *et al.,* 1996).

Ocimum sanctum

It is commonly known as Tulsi, an herbaceous plant found throughout the south Asian region. The plant widely cultivated in homes and temple gardens wild in India. Since ancient times, this plant is known for its medicinal properties. The aqueous extracted leaves of *O. sanctum* showed significant efficiency in reduction of blood sugar level in both normal and diabetic rats (Vats *et al*., 2002). Significant reduction of fasting blood glucose, uronic acid, cholesterol, amino acid, triglyceride and lipid indicated the hypoglycemic and hypolipidemic effects of *O. sanctum* in diabetic rats (Rai *et al*., 1997). The ethanolic extract of *O. sanctum* leaves has been reported in significant reduction of blood glucose in normal, glucose-fed hyperglycaemic and streptozotocin-treated diabetic rats. Also, renal glycogen increased 10 fold while skeletal muscle and hepatic glycogen levels decreased by 68 and 75% respectively in diabetic rats with compared to control rats (Vats and Yadav 2004). *O. sanctum* has also shown antibacterial, antifungal, antiviral, antiasthemitic, antitumor, antistress, antioxidant, antimutagenic and immunostimulant activities.

CONCLUSION

Prevalence of diabetes is increasing in all over the world, especially in developing country like India, at an alarming rate. Various factors, contribute to increase prevalence of diabetes include genetic factors that determine body fat distribution, glucose transport (GLUT) gene which is responsible for glucose transport, rapid changes in eating habits and lifestyles that are increasingly sedentary. Hypoglycemic effect in T2DM through stimulating or regenerating effects on β-cells. Diabetic stress and some other biological changes in tissue reduce by antioxidants in body (Sabu and Kuttan, 2013). Therefore, appropriate interventions in the form of weight reduction, changes in dietary habits, and increased physical activity could help in preventing the diabetes.

The insulin-responsive facilitative glucose transporter, GLUT gene, plays an extremely important physiologic role in the partitioning of glucose among peripheral tissues. In the normal cycle of fasting and refeeding, insulin is the key regulator of GLUT4 redistribution to the cell surface leading to increased glucose flux, yet the fate of glucose transported by GLUT4 is not completely understood. Restoration of GLUT gene levels enhance the uptake of glucose in liver and help to combat hyperglycemic conditions (Thorens *et al*., 1992). A second important role of glucose transport (GLUT) gene is to provide a mechanism of enhanced glucose uptake in working skeletal muscle, and also in adaptation of skeletal muscle to increased metabolic demand during periods of prolonged muscle contraction. Glucagon also raises blood glucose by stimulating gluconeogenesis, glycogenolysis and inhibiting glucose uptake by hepatic and muscle tissues. Diazoxide may be helpful as a daily treatment to raise the interprandial blood glucose.

Literature on the synthetic drugs for treatment of diabetes mellitus proved that mostly drugs have several side effects. Therefore, scientists are working to find out some safe and natural anti-diabetic agents that can cure the diabetes without side effects. Also, WHO has recommended the development of herbal medicine for the treatment of diabetes (Schmincke, 2003). Thus many different plants or their extracts have been used individually or in formulations as potential therapeutic agents in the treatment of diabetes and its complications. Traditional health care systems including herbal medicine are widely spread in developing countries, and the care of diabetic patients has been influenced by a growing interest in complementary and alternative medicines.

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