ABSTRACT

Glucose is a key fuel in mammalian cells that import by a process of facilitative diffusion mediated by glucose transporters (GLUT). A defect in GLUT expression for prolong time leads to diabetes mellitus. Medicinal plants used in traditional treatments confirm a possibility of tackling diabetes by regulating the GLUT activity in the body, with lesser side effects. Resistant of tissues to insulin is a major manifestation in type 2, and the cause can be localized in defect of glucose that can be reverse by medicinal plants. In vitro, in vivo, and in silico studies of plant extracts and its active compounds support for their multiple target mechanisms. Many medicinal plants used in the traditional medicine enhancing the translocation of GLUT and this could lead to a new approach for treating type 2 diabetes.

Keywords: Diabetes, Glucose transporters, Mechanism of glucose transporter, Glucose transporters 4, Medicinal plants.

INTRODUCTION

Since diabetes is a multifactorial disease leading to several complications, it demands multiple therapeutic approaches. Present oral therapeutics available for the treatment of type 2 diabetes mellitus (T2DM) has a single active constituent and target for specific mechanisms to act on [1]. However, there are certain limitations to these synthetic drugs due to their high cost and side effects [2,3]. Long back from Sushruta samhita medicinal plants are conserved as an esteemed source of drugs and becoming a growing part of modern biotech medicine. In contrast to synthetic drugs, herbal medications can target multiple mechanisms [4]. The medicinal plants being studied have varied mechanisms of action like:

- Lowering blood glucose level [5]
- Reducing oxidative damages [7]
- Insulin-mimetic agents and insulin-secretagogues [8]
- Improving insulin resistance and glucose tolerance [9]
- Up-regulation of glucose uptake [10]
- Activating various signaling pathways in the body and increasing the glucose transporter (GLUT) activity [12].

Many of the medicinal plants discussed help to improve GLUT activity in the body. Thus, the GLUTs from the plants are considered as most attractive targets for drug development [13]. The present article provides a comprehensive review on the antidiabetic plants that have been proved by the mechanism of action through GLUTs.

DIABETES AND GLUTS

The exploration of the role of GLUTs in diabetes is an area that is likely to produce considerable future advances. The detailed studies in rodents and human subjects revealed the significance of isoforms GLUT2, GLUT4 in peripheral insulin action [14], and regulation of whole-body glucose homeostasis. The failure of GLUT4 expression would represent a significant advance in the development of symptoms of diabetes. In type 2 diabetes patients, depleted the intracellular pool of GLUTs in adipose tissue has been identified [15]. Insulin resistance and diabetic conditions suggest that defective glucose transport in muscle may result from impaired translocation of GLUT4. These defects can be solved by other factors such as phosphorylation inhibitors, exercise, and hypoxia.

Stimulation of insulin receptor substrate-1 (IRS-1) phosphorylation and PI3 kinase activity in T2DM and, insulin-resistant states may contribute for the enhancement in GLUT4 translocation.

EFFECTS OF MEDICINAL PLANTS AND ITS ACTIVE CONSTITUENTS ON GLUT MECHANISM

After digestion, glucose uptake by peripheral tissues is one of the multiple mechanisms, which maintain blood glucose level in the body. Glucose uptake process involved in the activation of the GLUT in the liver, adipocytes, and skeletal muscle cells. Medicinal plants or their active constituents that can up-regulate GLUT expression and translocation that helps in the treatment of insulin resistance and hyperglycemia. Evidence from insulin-resistant rodent models suggests that defective glucose transport in muscle may result from impaired translocation of GLUT4 that can be effectively alleviated by conventional therapy. Hence, targeting this is the most gold promising goal for the treatment of type DM. This review provides the information on up-regulation of GLUT translocation by the isolated compounds and its medicinal plants which may help the researchers involved in this field to explore the mechanism of action unexplored medicinal plants.

ISOLATED ACTIVE PRINCIPLES AND CRUDE EXTRACT FROM MEDICINAL PLANTS ENHANCE GLUT ACTIVITY

Many medicinal plants studied have involved in the activation of PI3 kinase and subsequent phosphorylation and resulting in GLUT4 translocation. Some of the medicinal plants or its active compounds can enhance glucose uptake and up-regulation of GLUT4s are discussed below.

CINNAMALDEHYDE (CND)

Bioassay-guided fractionation of chloroform extract of Cinnamomum zeylanicum has performed by Anand et al., in 2010, and identified CND as an active principle against diabetes. Oral administration of CND to diabetic rats for 2 months showed significant improvement in muscle and hepatic glycogen content. In vitro incubation of pancreatic islets with CND enhanced the insulin release compared to glibenclamide. The insulinitropic effect of CND was found to increase the glucose uptake through GLUT4 translocation in peripheral tissues. The treatment also showed a significant improvement in altered enzyme activities of pyruvate kinase and phosphoenolpyruvate carboxykinase and their messenger RNA (mRNA) expression levels [16].
CND on GLUT4 gene expression in C2C12 skeletal muscle cells using real-time polymerase chain reaction (PCR) was done by Nikzamir et al. in 2014. In this, a significant increase in the expression of GLUT4 in CND treated cells was observed and thus supports for its previous study [17].

**GALLIC ACID (GA)**

Vishnu Prasad et al., in 2009, have identified and functionally characterized GA as the active principle from sea buckthorn leaf extract that increases glucose uptake in 3T3-L1 adipocytes. GA stimulates glucose uptake by inducing GLUT4 translocation in a wortmannin-sensitive but Akt-independent manner via atypical protein kinase Cζ/λ [18].

**PLUMBAGIN**

*Plumbago zeylanica* L. root is widely used in the traditional Indian medicine to treat DM. Plumbagin was isolated by Christudas Sunil et al. to explore their antidiabetic activity through glucose transporting mechanism. 15 and 30 mg/kg bwt of plumbagin were orally administered to streptozotocin-induced diabetic rats for 28 days. The compound significantly reduced the blood glucose and also altered all other biochemical parameters to normal. After treatment with plumbagin, enhanced GLUT4 mRNA and protein expression were observed in diabetic rats. In addition to this, it increased the activity of hexokinase and decreased the activities of glucose-6-phosphatase and fructose-1, 6-bisphosphatase significantly in treated diabetic rats. The results indicated that plumbagin enhanced GLUT4 translocation and contributed to glucose homeostasis [19].

**CHEMICAL CONSTITUENTS FROM EUCALYPTUS CITRIODORA HOOK LEAVES**

Wang et al., isolated compounds from *E. citriodora* to evaluate its ability to translocate GLUT4. *In vitro* cell-based GLUT4 translocation assay using stable L6 cells expressing pRFP-m orange cDNAs was performed. In this, betulinic acid and corosolic acid were the most active compounds, displaying 2.38- and 1.78-folds GLUT4 translocation enhancement, respectively. The tripenes oleanolic acid, ursolic acid, masadatic acid, and euscaphic acid, exhibited moderate GLUT4 translocation activity with 0.70-1.06-folds [20].

**4-HYDROXYPIPELIC ACID (4-HPA)**

4-HPA, isolated from the seed of *P. harmala* by G. Naras in 2012. Effect of 4-HPA on glucose uptake and GLUT4 translocation was investigated in L6 skeletal muscle cell lines. Treatment with 4-HPA stimulated both glucose uptake and GLUT4 translocation from intracellular to the plasma membrane in skeletal muscle cells in a concentration-dependent manner. These observations support that 4-HPA stimulate GLUT4 translocation through PI-3-Kinase-mediated insulin signaling pathway [21].

**NARINGENIN**

Zygmont et al., in 2010, reported that Naringenin stimulated glucose uptake in L6 myotubes in a dose- and time-dependent manner. It correlated with insulin in glucose uptake and did not increase glucose uptake in myoblasts. This result indicating that GLUT4 GLUTs may be involved in the naringenin-stimulated glucose uptake and suggested that naringenin increases glucose uptake by skeletal muscle cells in an AMP-activated protein kinase (AMPK)-dependent manner [22].

**BERBERINE**

Berberine, an isoquinoline alkaloid isolated from some Chinese medicinal herbs such as *Coptidis Rhizoma* and *Cortex Rhododendri* (So Hui KIM et al.). The treatment of berberine to 3T3-L1 adipocytes enhanced basal glucose uptake was noted in normal and in insulin-resistant state. Inhibition of phosphatidylinositols 3-kinase by the inhibitor wortmannin not disturbed the effect on basal glucose uptake and the expression of GLUT1 in 3T3-L1 treated cells. Moreover, berberine treatment increased AMPK activity in 3T3-L1 cells [23].

**CATECHIN**

Catechin isolated from methanolic stem extract of *Cassia fistula* which is used in the Indian medicine to treat diabetes. The mRNA expression of GLUT4 and protein was enhanced in skeletal muscle of diabetic rats. This study correlates with Docking study in Discovery Studio 2.1 shows the hypoglycemic effect and activates IR with peroxisome proliferator-activated receptor-gamma (PPARγ) [24].

**VANADATE AND TRIGONELLA**

Immunoblotting and immunohistochemistry studies showed that the treatment of diabetic rats with combined doses of vanadate and *Trigonella* seed powder are most effective in the plasma glucose homeostasis and enhances the GLUT4 expression in skeletal muscle [25].

**EMBELIN**

Embelin isolated from *Embelia ribes* significantly increased the PPARy expression in epididymal adipose tissue compared to diabetic control group and inhibited adipogenic activity. It moderately activates PPARy levels in the liver and skeletal muscle and also regulated insulin-mediated glucose uptake in epididymal adipose tissue through translocation and activation of GLUT4 in P3K/p-Akt signaling cascade [26].

**EPICATECHIN (EC) AND COCOA PHENOLIC EXTRACT (CPE)**

Both enhanced the tyrosine phosphorylation and total IR, IRS-1 and IRS-2 levels, and activated the PI3K/AKT pathway and AMPK in HepG2 cells. Phenolic extract of *Coca* enhanced the levels of GLUT2. EC and CPE enhanced the tyrosine phosphorylation and total IR, IRS-1 and IRS-2 levels, and activated the PI3K/AKT pathway and AMPK in HepG2 cells. CPE also enhanced the levels of GLUT2. In addition, EC- and CPE-regulated hepatic gluconeogenesis was prevented by the blockade of AKT and AMPK [27].

**GINSENOSIDE RH2**

Panax *ginseng* is a potential antidiabetic medicinal plant. Ginsenoside Rh2 increases the gene expression of GLUT4, at the mRNA and protein levels, in soleus muscle obtained from STZ-diabetic rats as a result of the increased β-endorphin secretion [28].

**TINOSPORA CORDIFOLIA AND ITS COMPOUND PALMITINE**

*T. cordifolia* is a well-investigated antidiabetic plant used in the Indian traditional medicine and also possessing several medicinal values. Sangeetha et al., in 2013, studied the mechanism of action of *T. cordifolia* and its active compound palmsite in differentiated myocytes. L6 cells which can enhance GLUT4 up to 5- and 4-fold, respectively and up-regulates PPARy 0.67- and 0.38-fold. Further, the inhibitors of insulin pathway prevented glucose uptake mediated by *T. cordifolia* and palmatine which shows that the activity is majorly facilitated through insulin pathway [29].

**AEGLE MARMELOS AND SYZYGIUM CUMINI**

*A. marmelos* and *S. cumini* are antidiabetic medicinal plants being used in the Indian traditional medicine. The dried powder was extracted sequentially using different organic solvents in increasing order of polarity and was analyzed for glucose uptake activity at each step. Methanolic extracts were found to be significantly active at 100 ng/ml dose comparable with insulin and rosiglitazone. Elevation of GLUT4, PPARy, and P3K kinase by these plants supported the up-regulation of glucose uptake. Hence, it was concluded that methanolic extracts of *A. marmelos* and *S. cumini* activate glucose transport in a P3K kinase-dependent fashion [30].

**ALLIUM SATIVUM, ALLIUM ASCALONICUM, SALVIA OFFICINALIS**

*A. sativum* (Garlic), A. ascalonicum (Persian shallot), and S. officinalis (Sage) have been used traditionally as antidiabetic herbal medicines.
An anti-diabetic effect of methanolic extracts of the above-mentioned three plants on alloxan diabetic rats was investigated. After 3 weeks of treatment by methanolic plant extracts, increased expression of insulin and GLUT4 genes in diabetic rats treated with these plant extracts was observed. *S. officinalis* reduced blood glucose in a similar way as acarbose and also intestinal sucrase and maltase activities were inhibited supports to their anti-diabetic activity [31].

**CINNAMON EXTRACT (CE) AND CINNAMON POLYPHENOLS (CP)**

CE and CP with procyandin type-A polymers exhibit the potential to increase the amount of protein tristetraprolin (TTP), IR, and GLUT4 in mouse 3T3-L1 adipocytes. Immunoblotting showed that CP increased IR levels and that both CE and CP increased GLUT4 and TTP levels in the adipocytes. Quantitative real-time PCR indicated that CE rapidly increased TTP mRNA levels by approximately 6-fold in the adipocytes. CE at higher concentrations decreased IR protein and mRNA level. These results suggest that cinnamon exerts the potential to increase the amount of proteins involved in insulin signaling, glucose transport, and anti-inflammatory or anti-angiogenesis response [6].

**ALOE VERA**

Densitometry scanning of agarose gel indicates an increase in GLUT4 transcripts by ~2.1764-fold by Aloe extract as compared to the control which is also comparable with Metformin (~4.4117-fold and insulin ~3.4779-fold. *In vivo* and *in vitro* studies of aqueous leaf extract of *A. vera* revealed that the glucose-lowering activities and some of its components facilitate GLUT4 mRNA expression. Up-regulation of GLUT4 mediated by stimulatory effects on the cytoskeletal proteins that help in vesicle trafficking during GLUT4 expression. The microtubule network and actin cytoskeleton by the link the signaling components or direct the vesicle movement to play a role in GLUT4 trafficking [32].

**TOONA SINENSIS**

Pei-Hwei et al., in 2008, tested the effects of *T. sinensis* leaf extract on alloxan-induced diabetic rats. Diabetic rats had lower expressions of GLUT4, mRNA, and GLUT4 protein in brown and white adipose tissues. In contrast, diabetic rats given the extract showed a significant increase in GLUT4 mRNA and protein levels that were analyzed through the Western blot and reverse transcription-PCR. Thus, the extract possesses an anti-hyperglycemic effect via an increment of insulin to mediate adipose GLUT4 [33].

**MOMORDICA CHARANTIA**

This is a well-reported antidiabetic plant with other pharmacological activities used in countries such as India and China. C-C. Shih et al., in 2009, demonstrated that bitter melon not only influences PPARγ-mediated pathway, which regulates adipocytokine gene expressions and also increases the numbers of GLUT4 at the cell surface, thereby promoting glucose uptake in peripheral tissue such as skeletal muscle, which is responsible for the major improvement of insulin resistance in fructose-fed rats. The extract increased the expression of PPARγ in white adipose tissue and decreased the expression of leptin that improved insulin resistance [34].

Another study was conducted by R. Kumar et al., in 2009. In this, the dose-dependent glucose uptake assay was performed on L6 myotubes. The combination of *M. charantia* with the aqueous and chloroform extracts of *M. charantia* fruit has shown the significant up-regulatory effect of GLUT4, PPARy, and PISK by 3.6-, 2.8-, and 3.8-fold, respectively. The up-regulation of glucose uptake was equivalent with insulin and rosiglitazone which was roughly 2-fold over the control [10].

**ABIES BALSAMEA, LARIX LARICINA, RHODODENDRON GRENLANDICUM, AND SARRACENIA PURPUREA**

These plants belong to Canadian medicinal plant species which possess their hypoglycemic activity through a common mechanism similar to that of standard drug metformin. These plants involved in the activation of AMPK-dependent pathway and alleviate insulin resistance with metabolic diseases in C2C12 murine skeletal myoblasts and H411E rat hepatocytes cells [35].

**TAMARINDUS INDICA**

The seeds of *T. indica* consist high levels of polyphenols and flavonoids. The treatment of aqueous seed extract for 4 weeks demonstrates that intracellular calcium and insulin release in isolated islets of Langerhans and improved the GLUT2 protein and SREBP-1c mRNA expression in the liver. Further, it increases GLUT4 protein and mRNA expression in the skeletal muscles of diabetic rats [36].

**ISOFLAVONE FROM PTEROCARPUS MARSUPIUM**

*P. marsupium* methanol extract activates the glucose transport in a PPARγ mediated P13 kinase-dependent fashion, and the *P. marsupium* isoflavone exhibits the same glucose transport activity by PPARγ mediated through P13 kinase-independent fashion in adipocytic cell line 3T3-L1 [37].

**CORNUS KOUSSA**

The leaves extract of *C. kousa* increases adipogenesis and the expression of PPARγ in 3T3-L1 adipocytes that led to significant stimulation of glucose uptake and insulin signaling, but not to AMPK signaling [38].

**PERSEA AMERICANA**

The hydroalcoholic extract of the leaves of *P. americana* decreased blood glucose levels and enhanced the metabolic state of the animals. PKB activation was observed in the liver and skeletal muscle of treated rats when compared with untreated diabetic rats. This result showed that the hydroalcoholic extract regulate glucose uptake in liver and muscles through PKB/Akt activation which determined by Western blot [39].

**FERMENTED TEA**

Administration of fermented tea for 7 days in male ICR mice strongly proposed that activates both P13K/Akt- and AMPK-dependent signaling pathways to enhance GLUT4 translocation. It increases the expression of IR to recover glucose intolerance [40].

**PINE BARK EXTRACT**

*In vitro* study revealed that the extract activating p38 mitogen-activated kinase which activates SGLT1 transporters. This transporter activates two different pathways of GLUT2 translocation in an inhibitory pathway involving P13 K mitogen-activated protein kinase or extracellular signal-regulated kinase [41].

**CECROPIA OBTUSIFOLIA**

Alonso-Castro et al., in 2008, studied the antidiabetic mechanisms of *C. obtusifolia* aqueous extract and its active principle. It stimulating glucose uptake in insulin-sensitive and insulin-resistant adipocytes. Thus, they might act by potentiating the insulin action or by activating a signaling pathway which is parallel to the insulin pathway [42].

**LYOPHYLLUM DECAREST**

Miura et al. in explained the antidiabetic activity of *L. decastes* in KK-Ay mice, an animal model of type 2 diabetes. The extract significantly reduced the insulin resistant and improved GLUT translocation [43].

**LIRIOPE PLATYPHYLLA**

Homoisoflavone from this plant increased insulin-induced glucose uptake in adipocytes. This uptake was mediated through the translocation of 36
GLUT4 to the plasma membrane and activates IRS-PI3K Akt signaling mechanism [44].

**ANDROGRAPHIS PANICULATA**

In vivo studies show that increased translocation of GLUT4 and α-glucosidase inhibition supports for their hypoglycemic effect which proves their multiple targets [45].

**AZADIRACHTA INDICA**

*A. indica* is an Indian medicinal plant. In vivo studies revealed that the hydroalcoholic extract exerted its hypoglycemic activity by increasing glucose uptake through GLUT, as well as glycogen deposition [46].

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**Table 1: Mechanism of action of medicinal plants on glucose transporters**

<table>
<thead>
<tr>
<th>Medicinal plant</th>
<th>Isolated compound/extract</th>
<th>Effect on GLUT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cortex cinnamomi</em></td>
<td>Cinnamaldehyde</td>
<td>Enhancements in GLUT4 gene expression with short-term treatment in C2C12 cell line studies [16]</td>
</tr>
<tr>
<td><em>Cinnamonum zeylanicum</em></td>
<td>Cinnamaldehyde</td>
<td>Immunoblot analysis shows restoration of GLUT4 protein in CND. <em>In vitro</em> analysis and <em>in vivo</em> analysis proves the translocation of GLUT4 [17]</td>
</tr>
<tr>
<td><em>Present in many plants</em></td>
<td>GA</td>
<td>GA stimulates GLUT4 translocation and glucose uptake in PKG/Lα dependent manner [18]</td>
</tr>
<tr>
<td><em>Hippophae rhamnoides sp. Plumago zeylanica (root)</em></td>
<td>Plumbagin</td>
<td>One Step RT-PCR and agarose gel electrophoresis in diabetic rats proved that plumbagin improves GLUT4 mRNA expression on skeletal muscle and restores the translocation of GLUT4 in diabetic rats [19]</td>
</tr>
<tr>
<td><em>Eucalyptus citriodora</em></td>
<td>Betulnic acid and corosolic acid</td>
<td>Increases the GLUT4 translocation by 2.38-folds in L6 myotubes when compared with control [20]</td>
</tr>
<tr>
<td><em>Peganum harmala Linn.</em></td>
<td>4-HPA</td>
<td>Enhanced expression of IRS-1 mRNA. 4-HPA stimulate GLUT4 translocation through PI-3-Kinase-mediated insulin signaling pathway in 57BL/Ks-j-db/db mice [21]</td>
</tr>
<tr>
<td><em>Present in citrus fruits and tomatoes</em></td>
<td>Naringenin</td>
<td>Berberine increases glucose transport activity of 3T3-L1 adipocytes by enhancing GLUT1 expression and also stimulates the GLUT1-mediated glucose uptake by activating GLUT1, a result of AMPK stimulation [23]</td>
</tr>
<tr>
<td><em>Coptidis Rhizoma and Cortex Phellodendri</em></td>
<td>Berberine (Lee et al. 2006)</td>
<td>Docking study in discovery studio 2.1 shows the hypoglycemic effect by the activation of Insulin receptor and PPARγ. Increase in both GLUT4 mRNA and protein proposes the involvement of Catechin to trigger the expression of the gene [24]</td>
</tr>
<tr>
<td><em>Cassia fistula</em></td>
<td>Catechin</td>
<td>Trigonella treatment increases the insulin levels due to stimulation of residual beta cells in diabetic rats and vanadate being an insulin-sensitizing agent augments the action of insulin on GLUT4 translocation [25]</td>
</tr>
<tr>
<td><em>Embelia ribes</em></td>
<td>Embelin</td>
<td>Increased the PPARγ expression in epididymal adipose tissue. And regulated insulin-mediated glucose uptake in epididymal adipose tissue through translocation and activation of GLUT4 in PI3K/p-Akt signaling cascade [26]</td>
</tr>
<tr>
<td><em>CPE</em></td>
<td>EC</td>
<td>EC and CPE strengthen the insulin signaling by activating key proteins of that pathway and regulating glucose production through AKT and AMPK modulation in HepG2 cells [27]</td>
</tr>
<tr>
<td><em>Panax ginseng</em></td>
<td>Ginsenoside Rh2</td>
<td>37</td>
</tr>
<tr>
<td><em>Tinospora cordifolia</em></td>
<td>Palmitate</td>
<td>The expression of PPARγ is up-regulated by palmitate and <em>Tinospora cordifolia</em>. Expression of PPARγ is down regulated by palmitate and <em>Tinospora cordifolia</em> treatment. The antidiabetic activity is mediated by promoting GLUT4 expression and also modestly by up-regulating PPARγ expression [29]</td>
</tr>
<tr>
<td><em>Aegles marmelos and Syzygium cumini</em></td>
<td>Methanolic extract</td>
<td>These plants augmenting the glucose transport by up-regulation of GLUT4, PPARγ and PI3 kinase [30]</td>
</tr>
<tr>
<td><em>Allium sativum, Allium ascalonicum, Salvia officinalis</em></td>
<td>Methanolic extracts</td>
<td>Densitometric scanning reveals that <em>Allium sativum</em> increases in Ins and GLUT4 genes transcripts by 0.57-fold and 1.21-fold than control. <em>Allium ascalonicum</em> proves the increase in Ins and GLUT4 gene 0.31, 0.71-fold, respectively. In vitro studies shown 0.19-fold increase in INS gene and 1.05-fold gain in GLUT4 gene expression [31]</td>
</tr>
<tr>
<td><em>Cinnamon extract</em></td>
<td>Polyphenols</td>
<td>Results confirmed the increased level of GLUT4 expression [32]</td>
</tr>
<tr>
<td><em>Aloe vera</em></td>
<td>Aqueous extract</td>
<td>Up-regulation of GLUT4 mediated by stimulatory effects on the cytoskeletal proteins that help in vesicle trafficking during GLUT4. The microtubule network and actin cytoskeleton other link the signaling components or direct the vesicle movement to play a role in GLUT4 trafficking [33]</td>
</tr>
<tr>
<td><em>Toona sinensis</em></td>
<td>Leaf extract</td>
<td>Increases glucose uptake in the 3T3-L1 adipocytes and mediates the GLUT4 translocation mechanism [34]</td>
</tr>
<tr>
<td><em>Momordica charantia</em></td>
<td>Fruit extract</td>
<td>Increases the expression of PPARγ in white adipose tissue. Increases the mRNA expression and protein of GLUT4 in skeletal muscle [34,10]</td>
</tr>
</tbody>
</table>

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MUSA SAPIENTUM AND HELICITERES ISORA

Docking study in Autodock 4 software shows hypoglycemic activity, improve glucose uptake; flavonones activate the kinase domain in IR tyrosine kinase to *M. sapientum* [47]. *H. isora* enhance translocation of GLUT through AMP kinase cascade system [48].

In *in vitro*, *in vivo*, and *in silico* studies investigated on various medicinal plants proves the effectiveness in the translocation of GLUT, which are summarized in Table 1.

**CONCLUSION**

DM and its secondary complications are due to impairment in the glucose uptake and GLUT translocation. Now, it is proven that...
Medicinal plant| Isolated compound/extract| Effect on GLUT
---|---|---
Abies balsamea, Alnus incana| Glucose uptake in C2C12 skeletal muscle increased by these plants through AMPK signaling pathway in 18 hrs of treatment. Phosphorylation of AMPK and ACC were increased up to 2.5- and 3.5-fold, respectively. The AMPK pathway converges with the insulin receptor pathway at the level of AS160 and in this way can induce the translocation of GLUT4. GLUT4 mRNA was increased in liver SREBP-1c mRNA concentrations of diabetic treated rats [36]. Isolavone of this plant exerts the same glucose transport activity in an alternate mechanism; PPAR mediated by P3 kinase-independent manner in adipocytic cell-line 3T3-L1 [37]. Results showed that increases the GLUT4 translocation through increased insulin signaling of 3T3-L1 adipocytes [38].
Clausena, Laxiraria Picea mariana, Pinus banksiana, Rhododendron groenlandicum, Sarracenia purpurea L, Sorbus decora Schneid| Aqueous seed extract
Tammarindus indica| Pterocarpus marsupium| Isoflavone
Cornus kousa| Persea americana| Hydroalcoholic extract
Fermented tea extract| The extract regulates glucose uptake in liver and muscles by the activation of PKB/Akt [39].
Pine bark extract| Cecropia obtusi folia| Aqueous extract
Lyophyllum decastes| Liriope platyphylla| Aqueous seed extract
Andrographis paniculata| Azadirachta indica| Hydroalcoholic extract
Musasapientum| Helicteres isora| Fruits

GLUT: Glucose transporter, Ga: Galli acid, CND: Cinnamaldehyde, PCR: Polymerase chain reaction, mRNA: Messenger RNA, 4-HPA: 4-hydroxypipecolic acid, IRS: Insulin receptor substrate-1, AMPK: AMP-activated protein kinase, PPAR: Peroxisome proliferator-activated receptor-gamma, CPE: Cocoa phenolic extract, EC: Epicatechin

traditional antidiabetic medicinal plants and their active constituents could enhance the GLUT translocation from an intracellular pool to the plasma membrane through signaling pathways. These plants could be used as efficient therapeutic agents with less harmful side effects and cost effective than synthetic drugs for controlling glucose homeostasis. There is an increasing evidence from the data reviewed in the current article suggests that the translocation of GLUT which can revive DM, therefore, may lead to the discovery of the next generation of antidiabetic drugs.

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