RESEARCH PAPER

Mechanistic Evaluation of Stevioside on Insulin Signaling Molecules in Gastrocnemius Muscle of Type 2 Diabetic Rats Using Histopathology, Gene Expression, and Molecular Docking Approaches

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ABSTRACT

Background: Impaired post-receptor insulin signaling plays a critical role in insulin resistance in Type 2 diabetes mellitus (T2DM). Key regulators of this pathway include insulin receptor (IR), insulin receptor substrate-1 (IRS-1), Akt, and glucose transporter 4 (GLUT4). Stevioside, a natural diterpene glycoside, has been reported to improve glucose homeostasis. This study investigated the mechanistic effects of stevioside on insulin signaling molecules in the gastrocnemius muscle of T2DM rats.

Methods: High-fat diet-induced diabetic rats were treated with stevioside (20 mg/kg). mRNA expression of IR, IRS-1, Akt, and GLUT4 was evaluated using RT-PCR and quantitative real-time PCR. Protein levels of IR, phosphorylated IRS-1, phosphorylated Akt, and GLUT4 were analyzed by Western blotting. Histopathological assessment of gastrocnemius muscle was performed using standard staining methods. Molecular docking of stevioside with IRS-1, Akt, and GLUT4 was conducted using PyRx (AutoDock Vina).

Results: Diabetic rats exhibited significant downregulation of IR, IRS-1, Akt, and GLUT4 at both mRNA and protein levels, along with marked muscle fiber degeneration. Stevioside treatment significantly restored gene and protein expression ($p < 0.05$), comparable to metformin-treated animals. Histological analysis showed improved myofibrillar architecture and reduced degeneration. Docking studies revealed strong binding affinities of stevioside with IRS-1 (−8.2 kcal/mol), GLUT4 (−7.8 kcal/mol), and Akt (−9.6 kcal/mol), indicating stable ligand–protein interactions.

Conclusion: Stevioside enhances skeletal muscle insulin signaling and GLUT4 expression, supporting its potential as a therapeutic agent for improving insulin sensitivity in T2DM.

Keywords: Stevioside, Insulin signaling pathway, Type 2 diabetes mellitus, GLUT4, Molecular docking.

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Introduction:

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion and insulin resistance in peripheral tissues. Insulin is the principal hormone regulating glucose homeostasis in response to elevated blood glucose levels (Lizcano and Alessi, 2002). Upon binding to its receptor, insulin activates a cascade of intracellular signaling events that regulate glucose uptake, lipid metabolism, protein synthesis, gene expression, cell growth, and survival (Rhodes and White, 2002). Normal glucose regulation requires adequate insulin secretion along with efficient glucose uptake and disposal in target tissues such as skeletal muscle, liver, and adipose tissue (Kutyavin and Chawla, 2016). Among these tissues, skeletal muscle

plays a predominant role in insulin-stimulated glucose utilization.

The insulin receptor (IR) is a transmembrane tyrosine kinase receptor composed of two extracellular α-subunits and two transmembrane β-subunits (Tiwari et al., 2007). It belongs to the receptor tyrosine kinase family and is abundantly expressed in metabolically active tissues including skeletal muscle (Lee and Pilch, 1994; Youngren, 2007). Binding of insulin to IR induces autophosphorylation of tyrosine residues, creating docking sites for downstream adaptor proteins such as insulin receptor substrates (IRS), particularly IRS-1 (Pirola et al., 2004; Bhaskar et al., 2012). Altered expression of IR and IRS-1 has been implicated in the pathogenesis of insulin resistance and T2DM (Saad et al., 1992; Zierath et al., 2000; Choi and Kim, 2010).

IRS proteins function as scaffolding molecules that recruit and activate key downstream signaling pathways including the phosphatidylinositol-3-kinase (PI3K)/Akt pathway and the Ras-MAPK pathway (White, 2002; Taniguchi et al., 2006). The PI3K/Akt pathway is particularly critical for mediating the metabolic actions of insulin. Activation of PI3K leads to the formation of phosphatidylinositol-3,4,5-triphosphate (PIP3), which recruits phosphoinositide-dependent kinase-1 (PDK1) and Akt to the plasma membrane (Copps and White, 2012). Full activation of Akt requires phosphorylation at Thr308 and Ser473 (Alessi et al., 1996; Dunn and Connor, 2011). Impaired Akt phosphorylation has been recognized as a major defect contributing to insulin resistance in skeletal muscle (Tremblay et al., 2001; Sylow et al., 2014).

One of the critical downstream targets of Akt is GLUT4, the principal insulin-responsive glucose transporter expressed in skeletal muscle and adipose tissue (James et al., 1988). Insulin stimulation promotes the translocation of GLUT4-containing vesicles from the cytoplasm to the plasma membrane, thereby facilitating glucose uptake (Czech and Corvera, 1999). Reduced GLUT4 expression and impaired translocation are well-established mechanisms underlying insulin resistance in T2DM (Karnieli et al., 2008). Therefore, restoration of the IR–IRS–PI3K–Akt–GLUT4 signaling cascade is essential for improving insulin sensitivity.

Stevioside, a natural diterpene glycoside derived from *Stevia rebaudiana*, has gained attention for its antihyperglycemic properties. Experimental studies suggest that stevioside enhances insulin secretion, improves glucose uptake, and modulates key molecules in the insulin signaling pathway. It has been reported to enhance GLUT4 translocation via activation of the PI3K/Akt pathway, similar to insulin action (Karlsson et al., 2005). Additionally, stevioside has been shown to reduce gluconeogenesis by inhibiting phosphoenolpyruvate carboxykinase (PEPCK), thereby lowering serum glucose levels (Mukherjee et al., 2010).

Despite emerging evidence, the mechanistic role of stevioside in modulating insulin signaling molecules in skeletal muscle requires further elucidation. The gastrocnemius muscle, being a major insulin-sensitive tissue, provides an ideal model to investigate molecular alterations in T2DM. Therefore, the present study aims to evaluate the effect of stevioside on key insulin signaling molecules including IR, IRS-1, Akt, and GLUT4 at gene and protein expression levels, supported by histopathological examination and molecular docking analysis to understand ligand–protein interactions at the structural level.

Materials and Methods

Experimental Animals and Treatment

High-fat diet–induced Type 2 diabetic rats were used for the study. Animals were divided into control and experimental groups, including diabetic, diabetic treated with metformin (50 mg/kg), and diabetic treated with stevioside (20 mg/kg). Gastrocnemius muscle tissues were collected for molecular and histological analyses.

Gene Expression Analysis

Total RNA was isolated from gastrocnemius muscle using TRIR (Total RNA Isolation Reagent). RNA purity was assessed spectrophotometrically (A260/A280 ratio >1.8). Complementary DNA (cDNA) was synthesized using reverse transcriptase (Eurogentec kit). Quantitative Real-Time PCR was performed using SYBR Green master mix (Takara Bio Inc., Japan) in a Stratagene MX3000P Real-Time PCR system. Gene-specific primers for insulin receptor (IR), insulin receptor substrate-1 (IRS-1), Akt, GLUT4, and β-actin (internal control) were used. Relative mRNA expression levels were calculated after normalization with β-actin.

Protein Expression Analysis

Protein extraction from plasma membrane and cytosolic fractions of gastrocnemius muscle was performed using RIPA buffer. Protein concentration was estimated by the Lowry method. Proteins were separated by SDS-PAGE and transferred onto PVDF membranes. Western blot analysis was performed to determine the expression of IR, p-IRS-1, p-Akt, and GLUT4 using specific primary antibodies and HRP-conjugated secondary antibodies. Protein bands were

visualized using enhanced chemiluminescence and quantified using Quantity One software. β-actin was used as a loading control.

Histopathological Examination

Gastrocnemius muscle tissues from all experimental groups were subjected to histopathological analysis to assess structural alterations and muscle fiber integrity.

Molecular Docking Analysis

The three-dimensional structure of IR (PDB ID: 1K3A) was retrieved from the Protein Data Bank. GLUT4 structure was generated by homology modeling using MODELLER 9v9.19. The structure of stevioside was obtained from the PubChem database. Molecular docking was performed using PyRx (AutoDock Vina) to evaluate binding affinity and hydrogen bond interactions between stevioside and target proteins.

Statistical Analysis

Data were expressed as mean ± SEM (n=6) and analyzed using one-way ANOVA followed by Student–Newman–Keuls multiple comparison test. A p-value <0.05 was considered statistically significant.

Instituional animal ethics committee clearance:

Animals were maintained as per the National Guidelines and Protocols approved by the Institutional Animal Ethics committee (BRULAC/SDCH/SIMATS/IAEC/02-2019/022 dated 25.02.2019).

Results and Discussion:

Table 1: Effect of Stevioside on insulin receptor IRmRNA, AKTmRNA, GLUT4 mRNA expression in gastrocnemius muscle of Type-2 diabetic rats

S.No	Parameters	Control	Control+ Stevioside (20mg)	Diabetes	Diabetes+ Met (50mg)	Diab+Stevioside (20mg)	P value
1	IR mRNA	1±0.0	1±0.05	0.63±0.03	0.93±0.03	0.8±0.05	P<0.0004
2	Akt mRNA	1±0.0	1.01±0.04	0.50±0.05	0.97±0.06	0.79±0.04	P<0.0001
3	GLUT4 mRNA	1±0.0	1.03±0.03	0.51±0.06	0.97±0.06	0.82±0.03	P<0.0001

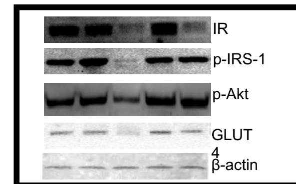
Table 2: Effect of Stevioside on IR, IRS-1, p-IRS-1 and GLUT 4 protien expression in gastrocnmius muscle of type-2 diabetic rats

S. no	Parameters	Control	Control+ Stevioside (20mg)	Diabetes	Diabetes+Met (50mg)	Diab+ Stevioside (20mg)	P value
1	p-IRS-1	70±5.77	77.67±7.21	37.67±1.45	80±2.88	56±3.05	P<0.0003
2	IR protein	120±5.77	126.7±8.81	71.67±4.41	128±9.16	92.33±3.93	P<0.0005
3	p-Akt	173.3±8.1	183.3±8.81	99.33±5.20	181.7±7.26	45.7±2.96	P<0.0001
4	GLUT4	72.67±3.1	81.67±4.41	47.33±3.93	88.33±6	71±3.786	P<0.0007

IN SILICO ANALYSIS

Table 3: Molecular Docking results of Stevioside with GLUT 4 & IRS-1.

Protein Name	Binding affinity (Kcal/mol)	H-bond details	Distance
GLUT 4	-7.8	GLN-113 TYR-168 TRP-173 ARG-188 ALA-190 ARG-336 GLU-359 GLY-404 TYR-405 ARG-433	2.3 2.5 2.2 2.3 2.3 2.6 2.1 2.2 2.6 2.0
IRS-1	-8.2	GLN-977 SER-979 LYS-1003 ASP-1105 ASN-1110	2.5 1.8 2.0 2.2 2.7



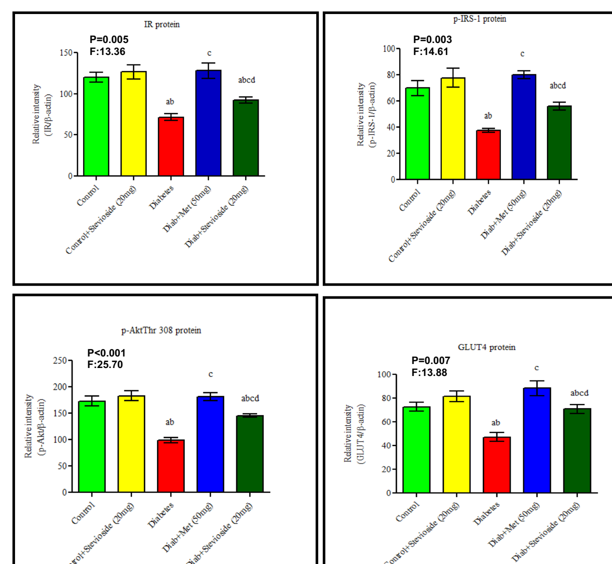


Figure 1: Effect of stevioside on IR, IRS-1, p-IRS-1 and GLUT 4 protein expression in gastrocnemius muscle of type-2 diabetic rats. Each bar represents mean ± SEM (n= 6) analyzed by one-way ANOVA with Student Newman Keul's multiple comparison test. Significance at *P <0.05,*
[a]Significantly different from control group.
[b]Significantly different from control rats treated with 20mg stevioside group
[c]Significantly different from diabetic group.
[d]Significantly different from metformin treated diabetic group.

Figure 2: Histology

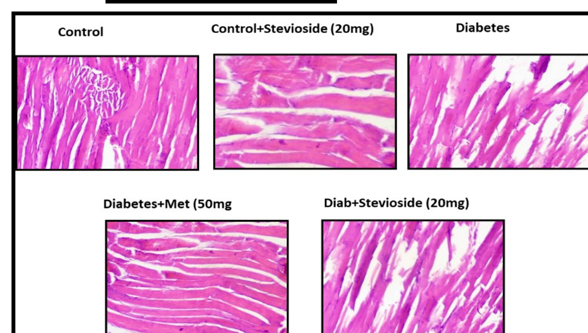
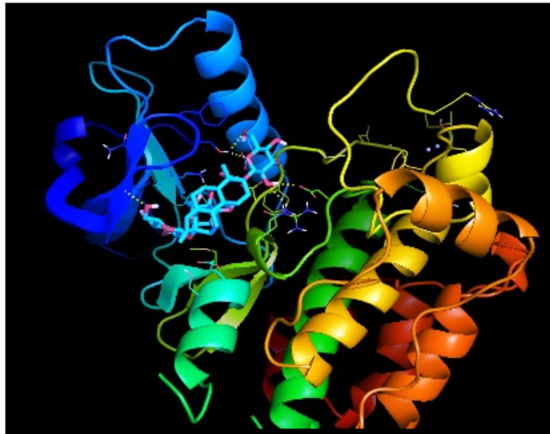


Figure 3: Binding interaction of Stevioside

Figure 4: Binding interaction of Stevioside with GLUT 4 Protein.



Insulin resistance in Type 2 diabetes mellitus (T2DM) is primarily associated with impaired post-receptor insulin signaling in skeletal muscle. The present study evaluated the effect of stevioside on key insulin signaling molecules in the gastrocnemius muscle of high-fat diet–induced Type 2 diabetic rats through gene expression, protein expression, histopathology, and molecular docking analyses.

Effect on mRNA Expression

A significant reduction in IR, IRS-1, Akt, and GLUT4 mRNA levels was observed in the gastrocnemius muscle of diabetic rats compared to controls ($p<0.05$). The decreased expression of these molecules explains the reduced insulin sensitivity and impaired glucose uptake characteristic of T2DM. Stevioside treatment (20 mg/kg) markedly restored IR, Akt, and GLUT4 mRNA expression levels toward normal values, comparable to metformin-treated animals. IRS-1 mRNA levels were also significantly increased in stevioside-treated diabetic rats. These findings indicate that stevioside improves insulin signaling at the transcriptional level.

Effect on Protein Expression

Western blot analysis revealed significant downregulation of IR, p-IRS-1, p-Akt, and GLUT4 proteins in diabetic animals. Reduced phosphorylation of IRS-1 and Akt confirms impairment of the PI3K/Akt pathway, a crucial mediator of insulin-stimulated glucose transport. Stevioside administration significantly increased the expression of IR, p-IRS-1, p-Akt, and GLUT4 proteins ($p<0.05$), suggesting restoration of insulin signaling and improved GLUT4 translocation. Stevioside-treated control animals did not show significant alterations, indicating its safety under normal physiological conditions.

Histopathological Findings

Histological examination of gastrocnemius muscle in diabetic rats demonstrated muscle fiber waviness, myofibrillar thinning, degeneration, and structural disruption. In contrast, stevioside-treated diabetic rats exhibited improved muscle architecture with reduced degeneration and restoration of normal muscle fiber structure. These findings correlate with improved molecular signaling and enhanced glucose uptake.

Molecular Docking Analysis

In silico docking studies demonstrated strong binding affinity of stevioside with key insulin signaling proteins. Stevioside showed binding energies of -8.2 kcal/mol with IRS-1 and -7.8 kcal/mol with GLUT4, forming multiple hydrogen bonds with critical amino acid residues. Additionally, stevioside exhibited high binding affinity with Akt (-9.6 kcal/mol), indicating stable ligand–protein interactions. The formation of hydrogen bonds at distances less than 3 Å confirms favorable molecular interactions. These results suggest that stevioside may directly interact with and modulate insulin signaling proteins at the structural level.

Discussion:

Insufficient post-receptor insulin signaling is well recognized as a major contributor to insulin resistance in Type 2 diabetes mellitus (T2DM), significantly impairing insulin-mediated metabolic activities (Mukherjee et al., 2010). Insulin is the principal hormone regulating glucose homeostasis, and its binding to the insulin receptor (IR) initiates a cascade of intracellular signaling events (Lizcano and Alessi, 2002; Rhodes and White, 2002). The IR, a transmembrane tyrosine kinase receptor abundantly expressed in skeletal muscle, undergoes autophosphorylation upon insulin binding, thereby activating downstream signaling molecules (Lee and Pilch, 1994; Tiwari et al., 2007; Youngren, 2007). Alterations in IR expression have been implicated in the pathogenesis of insulin resistance and T2DM (Saad et al., 1992; Zierath et al., 2000).

In the present study, diabetic rats exhibited significantly reduced IR mRNA expression, providing a molecular explanation for decreased insulin sensitivity. Stevioside treatment markedly restored IR mRNA levels, suggesting improved receptor-mediated insulin signaling. Since IR activation is essential for GLUT translocation from the cytosolic compartment to the plasma membrane, enhancement of IR expression may represent a primary mechanism by which stevioside improves glucose uptake (Pirola et al., 2004; Bhaskar et al., 2012).

Insulin receptor substrates (IRS), particularly IRS-1, function as adaptor proteins that transmit signals from IR to downstream pathways, including the phosphatidylinositol-3-kinase (PI3K)/Akt pathway (White, 2002; Taniguchi et al., 2006). Activation of

PI3K leads to the generation of phosphatidylinositol-3,4,5-triphosphate (PIP3), recruiting Akt to the plasma membrane (Copps and White, 2012). Full activation of Akt requires phosphorylation at Thr308 and Ser473 residues (Alessi et al., 1996; Dunn and Connor, 2011). Defects in Akt phosphorylation and reduced PI3K activity have been strongly associated with insulin resistance in both human and animal models (Tremblay et al., 2001). In accordance with these findings, diabetic rats in this study showed reduced Akt expression, whereas stevioside treatment significantly enhanced Akt mRNA levels, comparable to normal control animals, indicating restoration of downstream insulin signaling.

The glucose transporter (GLUT) family mediates facilitated diffusion of glucose across the plasma membrane (Czech and Corvera, 1999; Osbak et al., 2009). Among them, GLUT4 is the principal insulin-responsive glucose transporter in skeletal muscle and adipose tissue (James et al., 1988; Gospin et al., 2017). Insulin stimulation promotes GLUT4 vesicle translocation to the plasma membrane, thereby facilitating glucose uptake. Reduced GLUT4 expression and impaired translocation are well-established mechanisms underlying insulin resistance (Karnieli et al., 2008). In the present investigation, diabetic animals demonstrated a marked reduction in GLUT4 mRNA and protein expression, whereas stevioside treatment significantly elevated GLUT4 levels in gastrocnemius muscle. This improvement may be attributed to enhanced activation of the PI3K/Akt pathway.

Supporting evidence from previous studies indicates that steviol glycosides enhance GLUT4 translocation with efficacy comparable to insulin, mediated via activation of PI3K/Akt signaling and increased phosphorylation of pathway components (Karlsson et al., 2005). Furthermore, stevioside has been shown to reduce hyperglycemia by inhibiting gluconeogenesis through suppression of phosphoenolpyruvate carboxykinase (PEPCK), a rate-limiting enzyme in glucose production (Mukherjee et al., 2010). These findings collectively suggest that stevioside exerts multifaceted antihyperglycemic effects by improving both peripheral glucose uptake and hepatic glucose regulation.

Molecular docking analysis further substantiated the mechanistic role of stevioside. Docking studies using PyRx demonstrated strong binding affinity of stevioside with IR-S and GLUT4 proteins, exhibiting minimal binding energies and multiple hydrogen bond interactions. Hydrogen bond distances of less than 3 Å confirmed stable ligand–receptor complexes, suggesting direct structural interaction with insulin signaling molecules. These in silico findings complement the molecular and biochemical results; reinforcing the hypothesis that stevioside enhances insulin sensitivity through modulation of key components of the IR–IRS–PI3K–Akt–GLUT4 signaling axis.

Collectively, the present findings demonstrate that stevioside ameliorates insulin resistance by restoring IR expression, enhancing Akt activation, promoting GLUT4 transcription and protein expression, and strengthening ligand–protein interactions. The integration of molecular, biochemical, and computational evidence highlights the therapeutic potential of stevioside in the management of Type 2 diabetes mellitus.

Conclusion:

In conclusion, the present study demonstrates that stevioside significantly ameliorates insulin resistance in the gastrocnemius muscle of Type 2 diabetic rats by modulating key components of the insulin signaling pathway. Diabetes-induced reductions in insulin receptor (IR), Akt, and GLUT4 expression were effectively restored following stevioside treatment, indicating improved post-receptor insulin signaling and enhanced glucose uptake. The upregulation of PI3K/Akt pathway molecules and increased GLUT4 protein levels suggest improved insulin sensitivity at the molecular level. Histopathological findings further supported these molecular improvements by showing structural restoration of skeletal muscle tissue. Additionally, molecular docking analysis revealed strong binding affinity of stevioside with IR-S and GLUT4 proteins, reinforcing its direct interaction with insulin signaling targets. Collectively, these findings highlight the therapeutic potential of stevioside as a natural bioactive compound for improving skeletal muscle insulin signaling and glycemic control in Type 2 diabetes mellitus.

Conflict of Interest:

The authors declare no conflict of interest. This study was conducted as part of academic research, and no external commercial funding was received.

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