

Research article

Diosgenin promoted glucose uptake by attenuation of high glucose induced blockade of PI3K-Akt-GLUT4 pathway and ER stress

Ramesh Prajapath, Veeresh Kumar Sali, Meenakshi Bhardwaj, Malarvizhi R., Hannah R. Vasanthi

Natural Products Research Laboratory, Department of Biotechnology, Pondicherry University, Puducherry 605014, India

(Received: October 2023

Revised: November 2023

Accepted: December 2023)

Corresponding author: **Hannah R. Vasanthi**. Email: hannah.dbt@pondiuni.edu.in; hrvasanthi@gmail.com**ABSTRACT**

Introduction and Aim: Hyperglycemia is the signature style of type II diabetes (T2D) which impairs pathways of insulin signaling and endoplasmic reticulum (ER) stress. Diosgenin is a popular saponin known for its anti-diabetic and anti-obesity properties predominantly found in *Dioscorea* species. However, the mechanism of hypoglycemic effects related to pathways of ER stress, insulin signaling, and uptake of glucose in the liver gained less attention. Accordingly, this study was aimed to assess the effect of Diosgenin on the uptake of glucose, insulin signaling as well as on ER stress in human HepG2 cells cultured in hyperglycemic or high glucose (HG) condition.

Materials and Methods: Viability studies on HepG2 cells, assay for studying the uptake and consumption of glucose, gene expression, and docking studies were carried out.

Results: The treatment with Diosgenin was found to elevate the uptake as well as consumption of glucose in HepG₂ cells under hyperglycemic conditions. Diosgenin prevented inactivation of the PI3K-Akt pathway as well as GLUT4 levels induced by high glucose. Furthermore, endoplasmic reticulum stress elements viz., inositol requiring enzyme 1 (IRE1), protein kinase-like endoplasmic reticulum kinase (PERK), C/EBP homologous protein (CHOP) and sXBP1 were reduced by diosgenin treatment provoked by high glucose returning to normal ER homeostasis. Moreover, the effects are supported by the binding efficiency of diosgenin with insulin signaling proteins using bioinformatic tools.

Conclusion: Our findings suggest that diosgenin elevated the uptake of glucose by hindering the inactivation of PI3K-Akt-GLUT4 pathway and ER stress caused by high glucose, thus, preventing further hepatic dysfunction.

Keywords: Diosgenin; glucose uptake; insulin signaling; ER stress; high glucose.

INTRODUCTION

Hyperglycemia plays a principal role in sustaining metabolic dysfunction. The signature trait of type 2 diabetes (T2D) is hyperglycemia which is also noted in metabolic syndrome, CVD and a key determinant of tissue damage (1). Hyperglycemia upsets liver glucose, lipid, bile and triglyceride homeostasis, by various cellular processes such as decreased proteasome activity, reduced levels of molecular chaperones (2) including signal transduction, cytoskeleton regulation, protein folding and gene regulation. Hyperglycemia impairs liver function by inducing oxidative and nitrosative stress by oxidant-antioxidant imbalance (3); apoptosis induction (4) promotion of inflammation (5), activation of ER stress (6) and impairment of insulin signaling (7).

Insulin action begin with engagement with tyrosine kinase cell surface receptor, and insulin receptor (IR), which results in activation of tyrosine kinase activity setting a cascade of intracellular protein phosphorylation events activating downstream signaling effector proteins PI3K-Akt (5). The axis PI3K-Akt subsequently recruits GLUT4, the insulin responsive transporter, to the cytoplasmic membrane from its intracellular vesicle pool (8). Hyperglycemia also inhibits insulin signaling through PKC mediated

(7) inhibition of insulin receptor kinase activity with enhanced serine/threonine phosphorylation, PKR induced JNK mediated impaired insulin signaling (9) and TNF α associated decrease in insulin receptor tyrosine phosphorylation, and Akt serine phosphorylation (10).

Hyperglycemic conditions have been well studied for mediating Endoplasmic Reticulum (ER) stress (11). This in turn activates the canonical sensors such as ATF6, PERK, and IRE1 through the unfolded protein response (UPR), thereby restoring the ER homeostasis. Sustained activation of ER stress has a pathophysiological role in obesity, insulin resistance and type 2 diabetes (7). The mechanism of ER stress induced impairment of insulin action includes stress responses and signaling cascades. ER stress diminishes insulin signaling (12) by serine-phosphorylated IRS-1, inhibition of Akt activity by CHOP induction (13), and activation of JNK through via the IRE1 or the PERK/CHOP pathways, all of which result in impaired insulin receptor signaling (14). Taken together, in the state of hyperglycemia, both reduced insulins signaling, and ER stress occur and may influence each other, culminating in the further development of diabetic complications.

Diosgenin is a well-known steroidal saponin abundantly found in selected plant species like

Dioscorea, *Solanum*, and *Trigonella*. A wide range of pathological conditions such as inflammation, oxidative stress, dyslipidemia, apoptosis noted in diseases like cancer, CVD, diabetes and aging have been studied to be effectively treated with diosgenin (15). Several studies have demonstrated that diosgenin improves glucose metabolism through increase in muscular steroidogenesis (16), adipocyte differentiation, refining disturbed lipid profile (3), and modulatory effects on carbohydrate metabolism enzymes. Further, diosgenin is able to improve glucose metabolism by interference with insulin signaling via Estrogen receptor α (ER α), Estrogen receptor β (ER β) and reduced IRS1 serine phosphorylation induced by palmitate (17). These experimental evidences suggest that diosgenin may be able to affect dysfunctioning of insulin signaling and ER stress caused due to elevated glucose levels or hyperglycemia preventing the disease progress into type II diabetes and thereby prevent its associated complications. The PI3K/Akt/GLUT4 signaling pathway is the crucial downstream molecular pathway of insulin receptors and plays a key role in utilizing glucose. Therefore, this study aimed to assess and understand the effect of diosgenin on insulin signaling and ER stress under high glucose/hyperglycemic conditions and to unravel the associated mechanisms at the molecular level in HepG2 cells.

MATERIALS AND METHODS

Reagents

Diosgenin with a mentioned purity of 95% was procured from Sigma-Aldrich, USA. The compound was dissolved in a 3:1 cocktail of ethanol and DMSO. Insulin, DCFDA, RIPA buffer, and TRIzol reagent were procured from Sigma-Aldrich, USA. Protease inhibitor cocktail tablet was purchased from Roche Diagnostics. Glucose assay and LDH kit were from Spinreact, Spain. 2-NBDG was purchased from Cayman chemical, USA. DMEM, Fetal bovine serum, PBS, Trypsin, antibiotic and antimycotic solution, ethanol, DMSO, MTT, and DTT were all procured from Himedia, Mumbai. Anti-insulin receptors (sc-711), anti-PI3K (sc-423), anti-phospho-PI3K (sc-12929), anti-GLUT4 (sc-53566) were all purchased from Santa Cruz Biotechnology, CA, USA. Anti-phospho-Akt and Anti-Akt (#4691P) were obtained from Cell Signaling Technology, Beverly, USA.

Cell culture and treatments

Human hepatic cells; HepG2 were acquired from National Centre for Cell Science (NCCS), Pune. DMEM media supplemented with 10% FBS and antibiotic cocktail containing penicillin (100 units/mL) and streptomycin (100 μ g/mL) was used for culturing the cells. The cells were incubated in the standard conditions of 37° C and 5% CO₂ in a cell-culture incubator. Normal conditions of the cells were

maintained by culturing them in low glucose (LG) media (5.5 mM) while the hyperglycemic condition was established by culturing them in high glucose (25mM) in the presence or absence of diosgenin (DS) for 24h. After treatment the experiments were performed according to established protocols.

Cell viability studies

A 96-well plate was used to seed human HepG2 cells for performing the study and it was incubated at 37°C for 24h. Diosgenin in varied concentrations were added to the wells and further incubated for 24h. After treatment, the medium was replaced with MTT solution (5 mg/ml). Each well was added with 20 μ l of MTT reagent subjected to 4 h incubation period. 200 μ l of dimethyl sulfoxide (DMSO) was added to the wells to dissolve the formazan crystals. BioTek SynergyH1 microplate reader was used to record the absorbance values at a wavelength of 570 nm.

Glucose consumption assay

HepG2 cells seeded on to 24 well plates, upon reaching 90% confluence were changed to different culture media, low and high glucose, respectively and incubated for 24h. Based on the groups, cells were treated with diosgenin and incubated for a period of 24hrs. Glucose levels were measured using a glucose assay kit and the consumption of glucose was calculated by subtracting the glucose concentration of the wells with cells from the untreated blank groups.

Glucose uptake assay

2-NBDG treatment was used to analyze the uptake of glucose by the cells. Cells grown in 24-well plates were exposed to LG and HG and then were treated with diosgenin. Then cells were stimulated with or without insulin (150mM) for 20 min. 2-NBDG (50 μ M) treatments were given to cells in a glucose free medium for 20 minutes. After wash, excitation and emission fluorescence was measured at 485 and 535 nm respectively, using a microplate reader.

Western blotting

The cells with respective treatments and control groups were lysed with an ice-cold RIPA buffer. The lysed samples were then centrifuged at 4°C for 30 minutes and the supernatant was collected to estimate the protein concentration using BCA protein assay kit. A 10% SDS-PAGE gel was run to separate the proteins and blotted onto a PVDF membrane. Blocking was done for 4 h using 5% non-fat skimmed milk or BSA as blocking buffer. The membrane was added with a specific primary antibody and incubated overnight at 4°C, followed by 2 h incubation with corresponding secondary conjugates. ECL kit (Thermo Scientific) was used for visualizing protein bands using chemiluminescence and the band density was determined using ImageJ software.

Total RNA isolation and real-time PCR

The TRIzol method was used to extract RNA from the cells following the manufacturer's protocol. cDNA synthesis was carried out using High-Capacity cDNA Reverse Transcription Kit (Applied biosystems) using about 1µg of the total RNA. Gene expression was evaluated by performing quantitative real time PCR using SYBR green on Light Cyclor 96 system (Roche) following the standard conditions of initial 10 minutes preincubation at 95°C. Then, 40 cycles of pre-set specifications (initial denaturation for 10s at 95°C, annealing for 10s, and 72°C for 10s) were carried out. The relative expression levels were normalized to the expression of glyceraldehyde-3-phosphate dehydrogenase, which were used as internal controls. Table 1 enlists the primer sequences used for the study.

Table 1: Primer sequences of ER genes

Name	Primer sequence
PERK	Fwd:5'-TCACAGGCAAAGGAAGGAG-3' Rev: 5'-ACAACCTCCAAAGCCACCAC-3'
IRE1	Fwd:5'-GAGCTTGTTCTTGCTTTTG-3 Rev: 5'-ACCAGCCTCTATGCCTCTC-3'
sXBP1	Fwd:5'-GGAGTTAAGACAGCGCTTGG-3' Rev:5'-CTGGGTCCAAGTTGTCCAG-3'
CHOP	Fwd:5'-TGGAAGCCTGGTATGAGGAC-3' Rev:5'-TGTGACCTCTGCTGGTTCTG-3'

Molecular docking study

The molecular docking studies were done using Discovery Studio v3.1 (DS), Accelrys Inc., USA, 2013 (18). The structure of diosgenin was drawn using Marvin Sketch v6.0.5 and prepared using the "ligand preparation wizard" of DS. The crystal structures of the target proteins were obtained from the protein data bank (<http://www.rcsb.org/>)-PI3K (PDB ID: 3ENE), Akt (PDB ID: 3QKK), PPAR γ (PDB ID: 4XLD), protein tyrosine phosphatase 1B (PDB ID: 4Y14), and insulin receptor (5E1S). Then the 3D structures were submitted to WHATIF server for adding missing amino acid residues, hydrogen etc. After that, the protein was prepared using the protein preparation wizard of DS with default parameters. The Chemistry at Harvard Macromolecular Mechanics, Cambridge, USA (CHARMM) force field was utilized to optimize and minimize the target proteins at pH 7.4. The LibDock docking protocol with default parameters was then used to perform molecular docking of target proteins with diosgenin. The 2-D diagram of docking was derived to identify actual interacting receptor residues with bound ligands.

Statistical analysis

Results are expressed as means $\pm$ SD. Statistical significance was analyzed by one-way ANOVA with Tukey post hoc test (GraphPad Prism version 5). $P < 0.05$ was considered statistically significant.

RESULTS

Cell viability

The possible effect of diosgenin on the viability of the cells was studied by exposing HepG2 cells to various concentrations ranging from 0.001µM to 10µM for 24 h. The findings of the study revealed that the treatment of diosgenin did not induce changes in the viability of cells which was determined calorimetrically by MTT assay. The results indicated that the studied concentrations of diosgenin did not damage the integrity of the cells as evidenced in Fig. 1 and confirmed that HepG2 cells treated with diosgenin did not show any cytotoxicity.

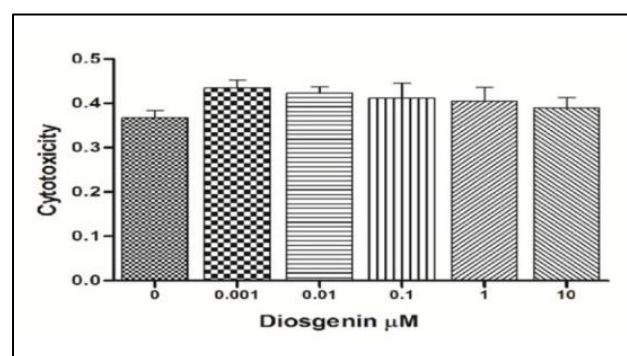


Fig. 1: The effect of diosgenin on cell viability in HepG2 cells

The data is represented as the mean $\pm$ SD, n=3.

Glucose consumption

Initially, the effect of diosgenin on insulin signaling pathway was examined at the cellular level by evaluating its role in glucose metabolism and observing its effects on glucose consumption in HepG2 cells. Glucose consumption in HepG2 cells was tested at various dosages based on the MTT assay. As compared to LG group a significant reduction in glucose consumption of HG model group was observed signifying that insulin resistance developed. The groups with low glucose (LG) conditions were found to have higher glucose consumption ($p < 0.001$) compared to the HG group after an incubation period of 24h. Compared with HG model group, diosgenin significantly enhanced glucose consumption in a dose-dependent manner as shown in Fig. 2.

HepG2 cells treated with varied concentrations of diosgenin and the untreated groups were incubated for 24 h, and the glucose-oxidase method was used to determine the glucose concentration of the medium. Maximal effect of diosgenin on glucose consumption was observed at 1µM dose ($p < 0.001$). These results show that the anti- hyperglycemic activity of diosgenin is modulated by the increased glucose consumption by HepG2 cells.

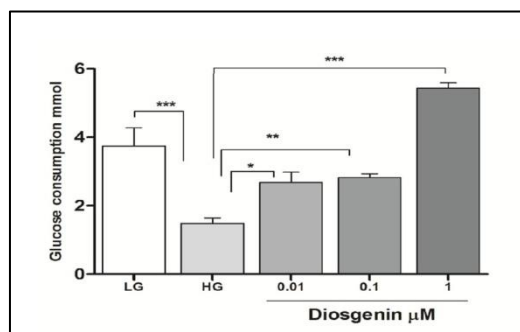


Fig. 2: Effect of diosgenin on glucose consumption in HepG2 cells

Data is represented as mean $\pm$ SD, n=3, ***p<0.001.

Glucose uptake

Glucose uptake studies were carried out to identify the effect of diosgenin by the uptake of glucose in HepG2 cells. The cells were treated with diosgenin with a range of concentrations for 24 h in the presence of HG culture medium to investigate the dose dependent effects of DS. Cells incubated in LG medium without DS represent normoglycemic conditions. As represented in Fig. 3, we found that HG decreased 2-NBDG uptake significantly (p<0.05) when compared to the LG group. 2-NBDG uptake in HepG2 cells had significantly (p<0.01) increased with treatment of diosgenin when stimulated with insulin.

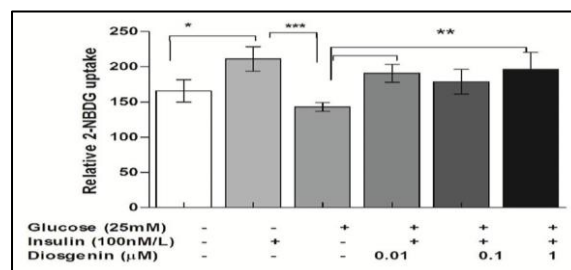


Fig. 3: Effect of diosgenin on glucose uptake in HepG2 cells

Data is shown as mean $\pm$ SD, n=3. *P<0.05 vs LG, p<0.01 vs HG. LG, low glucose; HG, high glucose

Interestingly cells treated with different doses of diosgenin had shown equal intensity of fluorescence. The results revealed that there was lesser uptake of 2-NBDG into HepG2 cells in HG treated cells than in the control groups while groups treated with diosgenin for 24h enhanced the uptake of glucose in HepG2 cells at all tested doses.

Effect of diosgenin on the expression of insulin stimulated PI3K/Akt/GLUT4-signaling pathway in the presence of high glucose

To understand the mechanism of diosgenin on improving glucose uptake, we explored the protein expression of insulin signaling pathways including insulin receptor, PI3K, Akt, and GLUT4. As shown in Fig. 4, in the present study, incubation of HepG2 cells in HG medium showed a significant reduction (p<0.001) in the expression of proteins downstream of the insulin receptor.

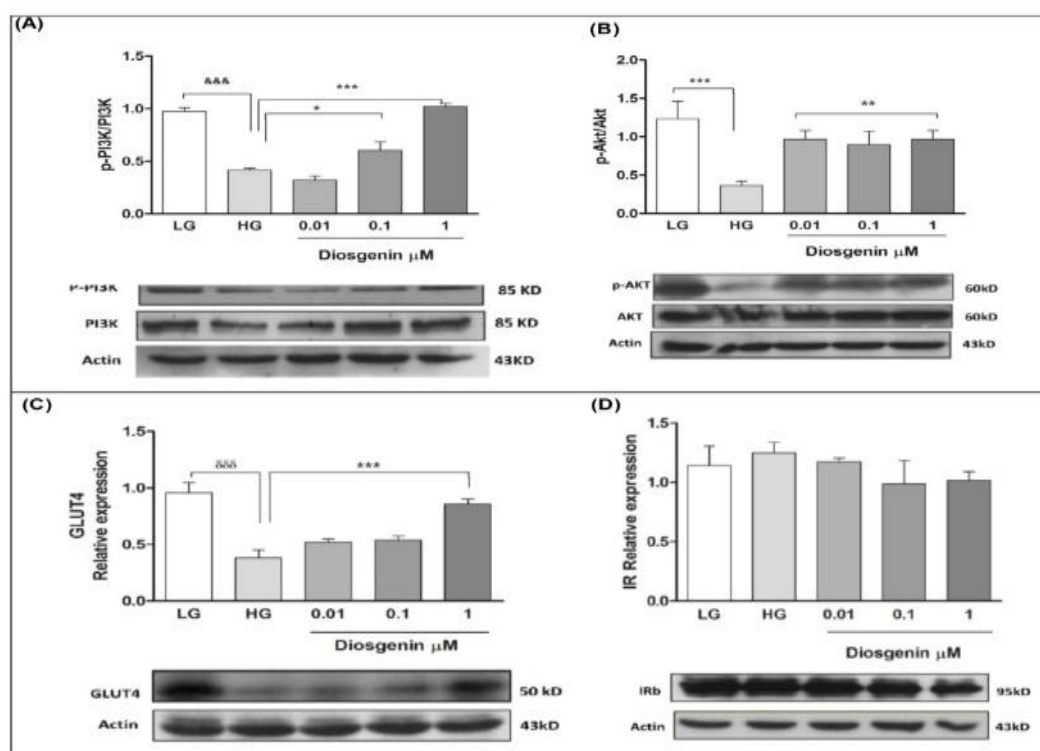


Fig. 4: Effect of diosgenin on insulin signaling in high glucose treated HepG2 cells

A: PI3K phosphorylation. B: Akt phosphorylation. C: Effect of Akt-stimulated GLUT4 translocation. D: IR expression. Data are represented as mean $\pm$ SD, n=3. ***p<0.001 vs HG. HG- high glucose.

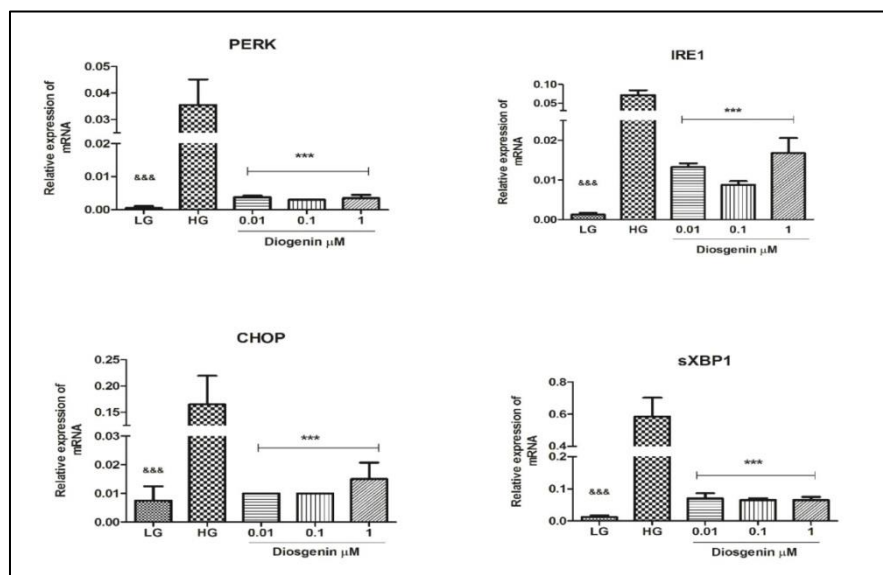


Fig. 5: Effect of diosgenin on high glucose induced ER stress in HepG2 cells. Data are represented by mean $\pm$ SD, $n=3$. *** $p<0.001$ vs HG. HG, high glucose.

Effect of diosgenin on the ER stress markers induced by high glucose

ER stress is one of the detrimental effects of hyperglycemic conditions. The mRNA expression profile of ER stress markers was quantitatively measured by real time PCR method. The ER stress markers PERK, IRE1, sXBP-1 and CHOP, were increased in the HG group, which represents hyperglycemic condition ($p<0.001$), compared to the levels observed in the LG group controls. The addition of diosgenin into HepG2 cells in the HG medium significantly decreased ($p<0.001$) the expressions of these ER stress markers. Fig. 5 shows the mRNA expression levels of ER stress genes. The data indicated that diosgenin involved in the inhibition of high glucose/hyperglycemia induced ER stress in HepG2 cells.

Molecular docking

To investigate the potential mechanism of diosgenin in glucose metabolism, molecular docking studies were performed using Discovery studio v3.1 in our study. Key targets that involve insulin signaling are selected

and evaluated for their molecular interactions with diosgenin. The docking results are summarized in Table 2.

The docking result revealed that diosgenin had interactions with all selected targets and is represented in Fig. 6. Docking of diosgenin on insulin receptor showed a single hydrogen bond formation in its active site at aspartate 1150 with a LibDock score of 102.41. Docking with PI3K showed that diosgenin formed two hydrogen bonds in the active site at Tyr867 and Thr887 with a LibDock score of 97.27. Diosgenin formed one hydrogen bond with Akt protein in its active site pocket at Asp74 with a strong LibDock score of 125.69. Similarly, the negative regulator of insulin signaling protein PTP1B formed two hydrogen bonds at Phe182 and Gln266 with diosgenin scoring of 110.07 in the LibDock program. PTP1B also showed Pi interactions. PPAR γ when docked with diosgenin showed a LibDock score of 114.05 by forming a single hydrogen bond with Arg288 in the active site.

Table 2: Details of LibDock scores, H-bond and interacted binding amino acid residues for diosgenin docked on insulin signaling proteins

Protein Target	No. of H-bonds	LibDock score	H-bond interacting residues	Amino acid residues
IR PDB 5E1S	1	102.41	Asp1150	Val1060, Met1076, Glu1077, Ala1028, Met1079, Leu1078, Met1139, Arg1000, Asp1083, Leu1002, Gly1082, Val1010, Gly1149
PI3K PDB 3ENE	2	97.27	Tyr867, Asp841	Ile879, Met953, Ala885, Trp812, Thr886, Thr887 Lys890, Met804, Ile963, Asp964,
Akt PDB 3QKK	1	125.69	Asp274	Leu295, Leu181, Asp292, Lys158, Lys179, Lys163, Gly157, Gly162, Gly159, Val164, Thr160, Phe161, His194
PPAR γ PDB 4XLD	1	114.05	Arg288	Ile281, Arg280, Gly284, Val277, Met348, Cys285, Leu333, Leu340, Phe264, Ile341, Ser342, Glu259,

PTP1B PDB 4Y14	1	110.07	Gln266	Arg221, Ile219, Gly220, Ala217, Tyr46, Asp181, Val49, Asp48, Ser216, Phe182, Gln262
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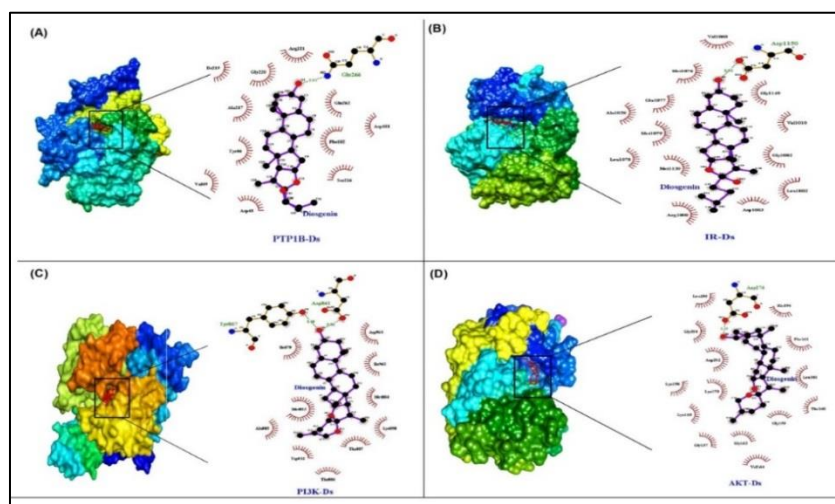


Fig. 6: Molecular docking simulation results of diosgenin with IR, PI3K, Akt and PTP1B. Surface model and 2D interaction diagrams between diosgenin and amino acid residues of proteins. A) Docking pose of diosgenin with PTP1B, B) docking pose of diosgenin with insulin receptor (IR), C) docking pose of diosgenin and PI3K and D) docking pose of diosgenin with Akt.

DISCUSSION

The importance of insulin signaling in liver cells is well appreciated, however, the adverse effects of high glucose on insulin signaling pathway in association with ER stress signaling has to be examined in the presence of an anti-diabetic/hypoglycemic agent, diosgenin. In the present study, we investigated the modulatory action of diosgenin on high glucose/hyperglycemia induced injury of the proximal events of insulin signaling in association with ER stress in human HepG2 cells.

The liver plays a crucial role in regulating the metabolism of energy nutrients throughout the body. When hyperglycemia occurs, it can harm the tissues that insulin targets, impairing the ability of insulin to initiate important metabolic processes. Consequently, one of the key indicators of hyperglycemia is disruption in hepatic metabolism, leading to a dysregulation of the insulin signaling pathway within the liver. HepG2 cells are commonly utilized in biochemical and nutritional research as they serve as a cell culture model for human hepatocytes, maintaining their structural and functional characteristics even in a cultured environment (19).

It has been shown that diosgenin has potent hypoglycemic activity. However, there is no direct evidence that diosgenin modulates insulin signaling in high glucose/ hyperglycemic conditions and its associated ER stress in human HepG2 cells. In this study, we demonstrated that diosgenin improved insulin resistance induced by high glucose/hyperglycemia in HepG2 cells through PI3K/Akt promoted glucose uptake and reduced ER stress caused by high nutrients. To understand the pharmacological effects of diosgenin, we conducted

experiments to measure glucose consumption and uptake in HepG2 cells exposed to a high glucose medium. Treatment of HepG2 cells with diosgenin led to a significant increase in both cellular glucose consumption and glucose uptake, as depicted in Figs. 2 and 3. These results suggest that the enhanced glucose uptake may contribute to the overall glucose consumption in the cells. This novel finding highlights the association between diosgenin and glucose consumption in HepG2 cells.

PI3 kinase/Akt signal pathway may be impaired due to the direct contribution of hyperglycemia (20). The metabolic effects of insulin are executed by the PI3K/Akt signal pathway, an indispensable tool for cells. The glucose transport apparatus of insulin signaling mainly includes PI3K, Akt, and GLUT4. Activation of PI3K/Akt is the essential step in insulin action downstream of the insulin receptor through a distinct signaling cascade connecting various enzymes (21). Activation of the insulin receptor triggers tyrosine phosphorylation of IRS that phosphorylates PI3K, which results in Ser/Thr kinase Akt activation. Akt stimulates translocation of the GLUT4, resulting in increased glucose uptake (22). Diosgenin treatment increased relative expressions of PI3K/Akt (Fig. 4) in HepG2 cells incubated with high glucose. Moreover, studies reported that diosgenin increased the expression of PI3K/Akt through ER α . However, the linkage between ER α and PI3K was not given in insulin resistance HepG2 cells (23). In a different study involving palmitic acid induced insulin resistance in endothelial cells diosgenin treatment activated PI3K/Akt through IRS-1 serine phosphorylation in a IKK β /NF- κ B dependent manner (17).

The maintenance of glucose homeostasis relies on

GLUT4, which is predominantly located in the intracellular membrane compartments. Previous reports showed that expression of GLUT4 improved insulin resistance and glucose utilization in HepG2 cells (24,25). In this study, we reported for the first time that diosgenin stimulates glucose uptake by translocation of GLUT4 (Fig. 4) involves an activated PI3K/Akt signaling pathway. These results are in line with the cellular glucose consumption and glucose uptake activity of diosgenin. These observations suggest that the hypoglycemic properties of diosgenin are attributed to its glucose consumption.

Deficit in energy and nutrients, variations in redox and calcium balance and increased demand for protein synthesis cumulates misfolded proteins overloading the ER above its capacity cause stress. This stress then affects various signal transduction pathways through a process known as the unfolded protein response (UPR) (26). ER stress is linked to development of metabolic disorders: obesity, T2D, insulin resistance, atherosclerosis, and heart and liver diseases (6). In the present study, we showed that high glucose elicited ER stress in HepG2 cells. High glucose increased the mRNA expression of PERK and IRE1 accompanied with their downstream target mRNA CHOP and sXBP1, respectively (Fig. 5). ER stress impairs proximal insulin signaling, through the increased serine and decreased tyrosine phosphorylation of insulin receptor substrate (IRS) 1, reduced Akt phosphorylation (27), reduced GLUT4 proteins, and mRNA levels (28). Diosgenin reduced the expression of ER stress markers in HepG2 cells. This ameliorating effect of diosgenin on ER stress could account for the improved insulin signaling and glucose consumption of insulin resistance HepG2 cells.

Docking studies showed that diosgenin had good binding affinities to all the selected protein targets which are related to insulin signaling. Diosgenin had predicted hydrogen bonding and hydrophobic interactions within the active sites of IR, PI3K, Akt and PTP1B which can be correlated with the docking score and the amino acid interactions.

There are still some limitations in our study. In this study, insulin receptor protein expression was not changed during LG, HG and diosgenin treatment. Also, the expression profile of PI3K and Akt is whether directly influenced by diosgenin or through inhibitory action on PTP1B and ER stress has required further experimental studies. Therefore, further study is required for the hypoglycemic effects of diosgenin using pharmacological inhibitors and expression studies.

CONCLUSION

The present study revealed that diosgenin promoted glucose uptake without cytotoxicity to HepG2 cells, and that these effects were mediated via PI3K-Akt-GLUT4 pathway. The ability of diosgenin on

improving glucose metabolism may relate to the inhibition of ER stress elements which includes PERK, IRE1, sXBP1 and CHOP induced by high glucose. Subsequently, insulin signal transduction may be magnified by inhibitory effect on PTP1B and enhancing phosphorylation of Akt. In summary, diosgenin exerted potent and beneficial hypoglycemic effects by inhibiting PTP1B and activating PI3K/Akt signaling pathways in insulin resistant HepG2 cells.

ACKNOWLEDGEMENT

This work was funded by DST-SERB project grant (SERB/F/0943/2011-2012), Govt. of India. Centre for Bioinformatics, Pondicherry University for providing facility for computational study: UGC (SAP) and DST (FIST) grant to Dept. of Biotechnology, Pondicherry University is also acknowledged for infrastructural facilities to carry out the present work. Fellowship from DST, Govt. of India, and Pondicherry University to the authors is also acknowledged. Further, the assistance of editing and proofreading the manuscript to the journal requirements by Mrs. Saranga Rajesh is acknowledged.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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