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Article

Syringin inhibits insulin resistance through the PI3K/AKT pathway

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ABSTRACT

This study aims to investigate the effects of syringin on insulin resistance (IR) and its mechanisms using an IR model in HepG2 cells. IR was induced by 10^4 mol L^{-1} insulin for 24 h, followed by syringin treatment at various concentrations for 48 h. Levels of glucose, triglycerides, TNF-α, IL-6, and GRP78 were measured, and protein expression of IRS-1, p-IRS-1, PI3K, p-PI3K, AKT, p-AKT, FoxO1, and p-FoxO1 was analyzed by Western blot. Compared with controls, the IR model showed significant increases in glucose, triglycerides, TNF-α, IL-6, GRP78, and decreases in p-IRS1/IRS1, p-PI3K/PI3K, p-AKT/AKT, with increased p-FoxO1/FoxO1 (all $p < 0.01$). Syringin (50–200 μg mL^{-1}) significantly lowered glucose, triglycerides, TNF-α, IL-6, and GRP78, and reversed these signalling changes by upregulating p-IRS1/IRS1, p-PI3K/PI3K, p-AKT/AKT and downregulating p-FoxO1/FoxO1 ($p < 0.05$). Syringin effectively ameliorates insulin resistance in HepG2 cells, lowers glucose and triglycerides, and improves glucose-lipid metabolism, likely via the PI3K/AKT pathway.

Keywords: syringin, insulin resistance, PI3K, AKT, HepG2

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INTRODUCTION

Insulin resistance (IR) is a condition characterized by decreased cellular or tissue response to normal doses of insulin and is a significant predisposing factor for multiple metabolic disorders, including obesity, type 2 diabetes (T2DM), and polycystic ovary syndrome (PCOS) (1). It plays a vital role throughout the progression of T2DM, and also contributes to the initiation and advancement of renal and cardiovascular diseases (2). In recent years, due to lifestyle changes, such as reduced physical activity and increased food availability, the incidence of IR-related diseases has risen significantly. According to literature reports, nearly 537 million adults globally are affected by diabetes, with the majority being T2DM. This figure is expected to rise to 783 million by 2045. Diabetes has become the third most prevalent disease after cancer and cardiovascular diseases (3). In addition to lifestyle changes, effective blood glucose control and the prevention of complications are essential for managing diabetes. Therefore, preventing and treating IR has become a significant focus of recent research.

IR is primarily attributed to various factors, with the most extensively studied being abnormalities within the insulin signalling pathway. In this pathway, insulin attaches to its receptor on the cell membrane, which undergoes autophosphorylation, activating its intrinsic tyrosine kinase activity. The activated insulin receptor subsequently phosphorylates the tyrosine residues of the intracellular insulin receptor substrate 1 (IRS1). The phosphorylated IRS1 binds to and interacts with the downstream phosphatidylinositol 3-kinase (PI3K) *via* its SH2 domain. Upon IRS1 binding to the p85 subunit of PI3K, the p110 catalytic subunit is released and activated. Activated PI3K catalyses the phosphatidylinositol-4,5-bisphosphate (PIP2) on the cell membrane to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 serves as an essential second messenger, recruiting downstream proteins with PH domains, such as AKT, to the cell membrane. AKT is a serine/threonine kinase that binds to PIP3 through its PH domain, leading to its translocation to the cell membrane. At this point, PDK1 phosphorylates AKT at the Thr308 site, and mammalian target of rapamycin complex 2 (mTORC2) phosphorylates AKT at the Ser473 site, leading to its full activation. Once activated, AKT translocates to the cell nucleus, where it phosphorylates specific serine/threonine residues

of the transcription factor fork head box protein O1 (FOXO1). Phosphorylated FOXO1 binds to the 14-3-3 protein and translocates from the nucleus to the cytoplasm, resulting in the loss of its transcriptional activity (4, 5). Abnormalities in any of these key molecules within the insulin signalling pathway may lead to IR. In cases of IR, the pathway is inhibited, leading to the accumulation of FOXO1 in the nucleus, which activates target genes and may result in metabolic abnormalities. This results in hyperglycemia by inhibiting gluconeogenesis and promoting glucose uptake. Furthermore, other factors affecting vital molecules in the insulin signalling pathway, such as increased expression of inflammatory factors like tumour necrosis factor alpha (TNF-α), due to obesity, endoplasmic reticulum stress (ERS), and oxidative stress, can inhibit the insulin signalling pathway (6).

Syringin, a natural product extracted from plants like *Syringa vulgaris* L. and *Acanthopanax*, has shown multiple biological functions, such as antioxidant, neuroprotective, anti-inflammatory, antiallergic, and antidiabetic effects (7). Animal studies suggest that syringin has hypoglycemic properties and can improve IR induced by a high-fat diet in rats, without affecting body mass. However, there is limited research on the specific molecular mechanisms underlying these effects. Most studies have primarily focused on syringing's influence on insulin secretion, with less attention given to its effects on insulin sensitivity.

In comparison, rosiglitazone (RSG), a well-known insulin sensitizer, improves lipid and glucose metabolism by activating peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ is highly expressed in adipose tissue, where it regulates adipocyte differentiation and energy storage. It is also expressed in the liver, and its overexpression can lead to lipid accumulation. Previous studies indicate that rosiglitazone can improve insulin resistance *in vivo* by increasing the expression of AKT and PI3K (8).

HepG2 cells, derived from human liver cancer, retain many functions of normal liver cells, including glucose metabolism, lipid synthesis, insulin signalling, and other key physiological processes. The liver serves as a principal, target organ for insulin action and plays an essential role in regulation of glucose. Therefore, HepG2 cells are suitable for simulating the IR in the liver. These cells are widely used to study the mechanisms of insulin resistance induced by various factors (9). This study aims to utilize HepG2 cells to develop an IR model (IR-HepG2 cells) by exposing them to high concentrations of insulin. The suppressive effects of varying concentrations of syringin on the insulin-resistant cell model, were investigated, along with its potential mechanisms. A variety of methods, including cell culture, drug intervention, cell viability assays, enzyme-linked immunosorbent assays (ELISA), and Western blot, was used

to systematically evaluate the effects of syringin on cellular metabolic state and associated signalling pathways, particularly its potential to improve IR.

EXPERIMENTAL

Reagents and antibodies

Syringin, rosiglitazone, and recombinant human insulin were obtained from Beijing Soley Bao Technology Co., Ltd. (China). The triglyceride assay kit was sourced from Nanjing Jiancheng Bioengineering Institute (China). The IL-6 ELISA kit, TNF-α ELISA kit were acquired from Lian Ke Biotechnology Co., Ltd. The GRP78 ELISA kit was acquired from Shanghai Yaji Biotechnology Co., Ltd. (China). RPMI1640 culture medium and fetal bovine serum were purchased from Gibco. Goat anti-rabbit secondary antibody was obtained from Shanghai Bi Yun tian Biotechnology Co., Ltd. (China).

Cell culture and establishment of the IR model

Human liver cancer cells (HepG2) were purchased from Procell Life Science Technology Co., Ltd. and cultivated in RPMI 1640 medium added with 10 % fetal bovine serum at 37 °C with 5 % CO_2. The cells were seeded into 6-well plates at a density of 1×10^5 cells per well, with three parallel replicates per group. The experiment was performed in triplicate. IR-HepG2 cells was induced by treating HepG2 cells with 1×10^{-6} mol L^{-1} insulin for 24 hours. Following the drug treatment, the cells were incubated for an additional 48 hours.

Cell viability assay

The HepG2 cells were cultivated in a 96-well plate at a density of 1×10^4 cells per well, and they were exposed to 1×10^{-6} mol L^{-1} insulin for a whole day. After 48 hours of treatment with rosiglitazone (40 μg mL^{-1}) and syringin at concentrations of 50, 100, and 200 μg mL^{-1}, cell viability was assessed using the CCK-8 assay. The plate was incubated for two hours at 37 °C after 10 μL of CCK-8 solution was added to each well. A microplate reader was employed to measure absorbance at 450 nm. Each experiment was performed in triplicate.

Measurement of triglycerides and glucose content following syringin intervention

HepG2 cells were seeded at 1×10^4 cells per well in a 24-well plate and treated with 1×10^{-6} mol L^{-1} insulin for 24-hour period. The following treatment groups were included: blank control group, model group, rosiglitazone group (40 μg mL^{-1}), low-dose syringin group (50 μg mL^{-1}), medium-dose syringin group (100 μg mL^{-1}), and high-dose syringin group (200 μg mL^{-1}). The cell culture media were taken out after the 24-hour treatment period, centrifuged at 250

g for 10 min, and the supernatant solution was examined. The glucose and triglyceride content in the cell culture supernatants was measured using glucose oxidase and glucose-6-phosphate oxidase-peroxidase (GPO-PAP) enzyme methods, respectively.

Measurement of TNF-α, IL-6 and GRP78 content following syringin intervention

The levels of TNF-α, IL-6 and GRP78 in the cell culture supernatants were measured using ELISA. For TNF-α, a specific anti-human TNF-α antibody was precoated on a high-affinity enzyme plate. The plate was incubated with standards, test samples, and biotin-labelled detection antibodies. After washing to remove unbound substances, horseradish peroxidase-labelled streptavidin was added, followed by the addition of 3.3',5,5'-Tetramethylbenzidine (TMB) substrate for colour development in the dark. The colour intensity was positively correlated to the TNF-α concentration, and was measured by absorbance at 450 nm (reference wavelength 570–630 nm). The same procedure was used for IL-6 and GRP78.

Western blot analysis of IRS1, p-IRS1, PI3K, p-PI3K, AKT, p-AKT, FoxO1 and p-FoxO1 expression in HepG2 cells

The experimental groups were consistent with measurement of triglycerides. Following treatment, HepG2 cells were gathered, and total protein was separated using RIPA lysis buffer. Protein concentration was verified using the BCA assay. Proteins were denatured and detached by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), followed by transfer to a polyvinylidene fluoride (PVDF) membrane. The membrane was blocked with 5 % non-fat milk and incubated with primary antibodies for IRS1, p-IRS1, PI3K, p-PI3K, AKT, p-AKT, FoxO1 and p-FoxO1 at 4°C for two hours. Subsequently, the membrane was incubated with secondary antibodies at room temperature for two hours. Protein bands were identified with enhanced chemiluminescence (ECL) luminescence, and band intensities were examined using ImageJ software.

Statistical analysis

The experimental results were evaluated using SPSS version 18.0. The measurement data are expressed as means ± SD. A one-way analysis of variance (ANOVA) was employed to compare the mean values across different groups. A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCCUSION

Establishment of IR cell lines

Insulin, secreted by β cells, exerts its effects on target tissues such as the liver, muscles, and adipose tissues by promoting glucose uptake, utilization, and storage, while concurrently inhibiting endogenous glucose production, thereby reducing blood glucose. Conversely, when β cells are damaged, their function is compromised, or insulin target organs develop IR, glucose uptake and metabolism are impaired, resulting in hyperglycemia. Consequently, blood glucose levels can directly reflect the degree of IR (10). In this study, HepG2 cells were utilized to develop an IR model by administering a 1×10^{-6} mmol L^{-1} insulin solution for a period of 24 hours. It has been observed that the presence of IR in HepG2 cells primarily leads to impaired glycogen synthesis, an inability to control glucose production, and is closely associated with the onset of hyperglycemia (11).

The successful establishment of the IR HepG2 cells were confirmed *via* Oil Red O staining (Fig. 1). The nuclei of cells in both experimental and blank control groups appeared deep blue, while lipid droplets in the insulin-induced HepG2 cells stained red, indicating significant lipid accumulation in contrast to the blank control group. This observation confirms the induction of IR.

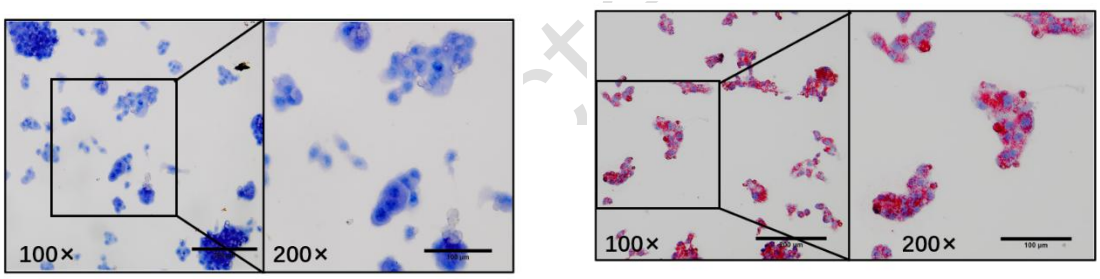

Fig. 1. Oil Red O staining of HepG2 cells before and after modelling: a) Oil Red O staining of HepG2 cells in the blank control group at 100× and 200×; b) Oil Red O staining of HepG2 cells after 24 hours of induction with 1×10^{-6} mol L^{-1} insulin at 100× and 200×. The cell nuclei of both the experimental group and the blank control group appeared dark blue, while in the HepG2 cells induced by insulin, the lipid droplets aggregated and showed a red colour.

Determination of glucose consumption after modelling

Following the induction of HepG2 cells with 1×10^{-6} mol L^{-1} insulin for 24 hours to create the IR-HepG2 cell model, a significant increase in the glucose consumption rate was detected compared to the blank control group (Fig. 2).

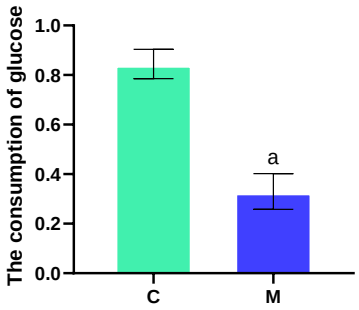

Fig. 2. The glucose consumption of IR-HepG2 cells. IR-HepG2 cells were induced by treating HepG2 cells with 1×10^{-6} mol L^{-1} insulin for 24 hours. The glucose consumption of IR-HepG2 was quantified using the glucose oxidase method. Compared with the blank control group, the rate of glucose consumption significantly increased. Results are shown as means ± SD; $p < 0.01$; C – control; M – model.

Effects of syringin on the proliferation of HepG2

Cell viability was assessed following treatment with syringin at concentrations of 50, 100, and 200 μg mL^{-1}. As shown in Fig. 3, no statistically significant differences were observed in cell proliferation, among the syringin-treated groups (50, 100, and 200 μg mL^{-1}) when compared to the blank control group ($p > 0.05$).

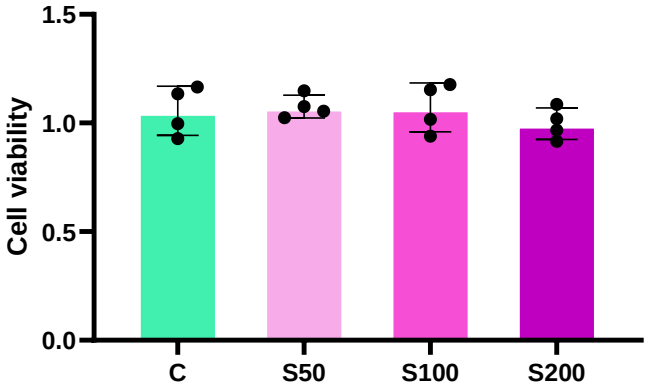

Fig. 3. Cell viability measurement. After establishing the insulin resistance model in HepG2 cells, different concentrations of syringin (50, 100, and 200 μg mL^{-1}) were applied to the cells. The CCK8 assay was employed to assess cell viability, with the proliferation potential quantified as a ratio relative to the untreated control. Results are shown as means ± SD; C – control; S50 – syringin 50 μg mL^{-1}; S100 – syringin 100 μg mL^{-1}; S200 – syringin 200 μg mL^{-1}.

Measurement of glucose and triglyceride content after syringin intervention

An increase in intracellular triglyceride (TG) content is recognized as a contributing factor to IR. The accumulation of triglycerides in tissues other than the liver and muscles is considered a significant determinant of IR (11). Physiological levels of insulin facilitate the uptake of free fatty acids (FFA) by HepG2 cells and enhance triglyceride synthesis, while elevated insulin concentrations can result in excessive FFA uptake by cells. Excessive FFA serves as a substrate that activates enzymes involved in triglyceride synthesis, such as diacylglycerol acyltransferase (DGAT), thereby promoting triglycerides accumulation within cells and the formation of lipid droplets. Elevated TG levels can induce IR through various mechanisms, and IR can disrupt the normal regulation of TG metabolism by insulin, forming a vicious cycle. Therefore, reducing intracellular TG levels may alleviate IR. According to literature, astragaloside IV ameliorates IR in HepG2 cells by inhibiting protein tyrosine phosphatase 1B and reducing TG accumulation (12). Forsythoside counteracts palmic acid-mediated IR in HepG2 cells by reducing oxidative stress and TG accumulation (13). In this study, following 24 hours of insulin induction (1×10^{-6} mol L^{-1}), cells were subsequently treated with syringin at concentrations of 50, 100, and 200 μg mL^{-1} for 48 hours. The levels of glucose and triglyceride in the cell culture supernatants were measured using glucose oxidase and GPO-PAP enzyme methods. As illustrated in Fig. 4, the model group exhibited significantly elevated glucose and triglyceride levels compared to the control group ($p < 0.05$). Conversely, the groups treated with syringin showed a significant reduction in glucose and triglyceride levels compared to the model group ($p < 0.05$).

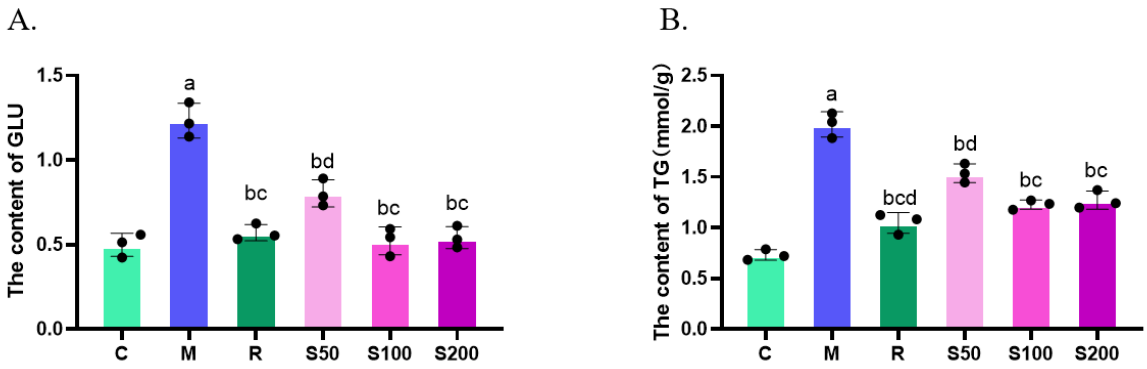

Fig. 4. Measurement of intracellular glucose and triglyceride content after syringin intervention. After HepG2 cells were treated with different concentrations of syringin (50, 100, and 200 μg mL^{-1}) for 48 hours, the content of: a) glucose and b) triglycerides was measured using glucose oxidase and GPO-PAP enzyme methods. Results are presented as means ± SD; a – $p < 0.05$, compared to the control group; b – $p < 0.05$, compared to the

model group; c – $p < 0.05$, compared to the S 50 group; d – $p < 0.05$, compared to the syringin S100 group; C – control; M – model; R – rosiglitazone; S50 – syringin 50 μg mL^{-1}; S100 – syringin 100 μg mL^{-1}; S200 – syringin 200 μg mL^{-1}.

Measurement of TNF-α, IL-6 and GRP78 content after syringin intervention

Multiple studies have highlighted a strong association between chronic inflammation and the onset of IR. Both Obesity and T2DM diabetes are characterized as low-level chronic inflammatory conditions, as they enhance the secretion of pro-inflammatory cytokines, activate inflammatory signalling pathways, and impair the insulin signalling pathway, thereby contributing to IR (14). TNF-α is a pro-inflammatory factor significantly implicated in the development of IR (15). HepG2 cells possess the capability to produce TNF-α, exhibiting low secretion levels under basal conditions, which increase under inflammatory and lipid accumulation stimuli. The autocrine production of TNF-α may play a role in the inflammatory response and metabolic disorders, such as insulin resistance, within these cells. Lipid accumulation in HepG2 cells can induce lipid toxicity, which in turn activates the inflammatory pathway and promotes TNF-α expression (16). As illustrated in Fig. 5, the levels of TNF-α were significantly increased in the model group in contrast to the control group ($p < 0.01$). Conversely, the content of TNF-α in each syringin intervention group was significantly decreased compared to the model group ($p < 0.05$). The findings of this study indicate that insulin stimulation of HepG2 cells results in a significant increase in TNF-α levels, suggesting that insulin can enhance the inflammatory response within the cells, thereby inducing IR. Conversely, the TNF-α content within IR-HepG2 cells is significantly reduced following the administration of syringin, indicating that syringin can decrease TNF-α secretion in IR cells, thereby mitigating IR.

Interleukin-6 (IL-6) is a cytokine with pleiotropic effects, playing a vital role in inflammatory responses and metabolic regulation (17). Previous studies indicate that IL-6 activates the Signal Transducer and Activator of Transcription 3 (STAT3) pathway, inhibits IRS-1 function, and reduces insulin-mediated glucose uptake. Concurrently, it upregulates the expression of key gluconeogenesis enzymes, such as, G6Pase, thereby increasing hepatic glucose output, and exacerbating IR (18). HepG2 cells are capable of secreting IL-6 under inflammatory or metabolic stress, with its level correlating to the extent of lipid accumulation within the cells. In states of insulin resistance, metabolic disorders, such as oxidative stress, ERS further stimulate IL-6 synthesis and release. The secreted IL-6 then acts on HepG2 cells

via autocrine mechanisms, strengthening the inflammatory response and IR, and can also influence the metabolic functions of adjacent liver, adipose tissue, and muscle tissue through paracrine mechanisms (19). The findings of this study demonstrate that following insulin stimulation, IL-6 expression in the cell culture supernatants significantly increases ($p < 0.01$). However, the IL-6 content is notably reduced following the administration of syringin ($p < 0.05$), suggesting that syringin can reduce IL-6 expression within cells, thereby mitigating IR.

GRP78 (Glucose-regulated Protein 78) is one of the most important molecular chaperones in ERS, facilitating proper protein folding and maintaining endoplasmic reticulum homeostasis. It plays a key role in the onset and progression of IR in hepatocytes. In unstressed HepG2 cells, GRP78 predominantly resides in the endoplasmic reticulum, with minimal release into the extracellular space. However, upon encountering ERS, such as oxidative stress or high glucose/high fat stimuli, cells activate the unfolded protein response (UPR), leading to marked increase in GRP78 expression. Some GRP78 is secreted into the extracellular space *via* non-classical pathway involving the Golgi apparatus, resulting in elevated GRP78 levels in the culture medium (20). Research indicate that metformin can inhibit the expression of ERS protein GRP78, modulate IRS-1phosphorylation, and protect hepatocytes from IR induced by saturated fatty acids (21). Additionally, pancreatic inhibitory factor inhibitors activate AMPK signalling through GRP78 activation, thereby improving lipid homeostasis, and enhancing insulin sensitivity by inhibiting PKC activity (22). The findings of this study demonstrate that, the levels of GRP78 were significantly increased in the model group in contrast to the control group ($p < 0.01$). compared to the model group, the expression of GRP78 in IR-HepG2 cells is significantly reduced following the administration of syringin. This suggests that syringin can enhance GRP78 activity, promote protein folding, alleviate ERS, and consequently improve insulin sensitivity.

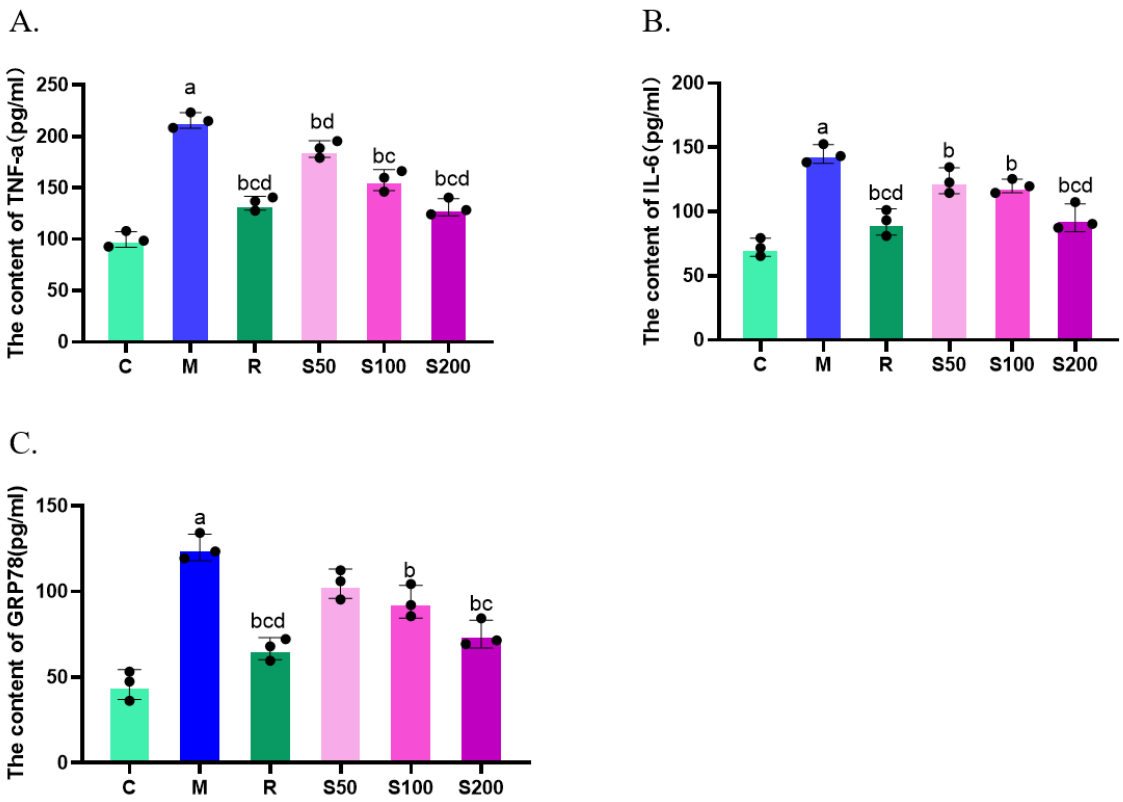

Fig. 5. Measurement of intracellular TNF-α, IL-6 and GRP78 content after syringin intervention. After establishing the IR model, the levels of: a) TNF-α; b) IL-6 and c) GRP78 were measured using ELISA, following treatment of HepG2 cells with different concentrations of syringin (50, 100, and 200 μg mL^{-1}) for 48 hours. Results are presented as means ± SD; a – $p < 0.01$, compared to the control group; b – $p < 0.05$, compared to the model group; c – $p < 0.05$, compared to the S50 group; d – $p < 0.05$, compared to the S100 group; IR – insulin resistance; C – control; M – model; R – rosiglitazone; S50 – syringin 50 μg mL^{-1}; S100 – syringin 100 μg mL^{-1}; S200 – syringin 200 μg mL^{-1}.

Expression of IRS1, p-IRS1, PI3K, p-PI3K, AKT, p-AKT, FoxO1 and p-FoxO1 proteins after syringin intervention

The activation of the PI3K/Akt pathway is pivotal in ameliorating IR. Upon insulin binding to receptors on hepatic cell surfaces, IRS1 is recruited and its tyrosine residues are phosphorylated, subsequently activating PI3K. PI3K, an intracellular phosphatidylinositol kinase with serine/threonine (Ser/Thr) kinase activity, upon phosphorylation, facilitates the phosphorylation of Akt at the Ser473 site. Akt, through the phosphorylation and inhibition of FoxO1, further inhibits the expression of gluconeogenesis genes, thereby reducing endogenous glucose production (5). In this study, Western blot analysis was performed to evaluate the

expression levels of PI3K, p-PI3K, IRS1, p-IRS, AKT, p-AKT, p-FoxO1, and FoxO1 proteins following syringin treatment (Fig. 6). Compared to the control group, the model group exhibited significantly lower levels of p-IRS1/IRS1, p-PI3K/PI3K, and p-AKT/AKT, along with higher levels of p-FoxO1/ FoxO1 ($p < 0.05$) indicating that IR can inhibit the PI3K/AKT pathway. In the model group, insulin signal transmission was obstructed, leading to decreased glucose conversion and utilization within the cells, thereby initiating and exacerbating IR. However, in the syringin-treated groups, there was a significant increase in the expression of p-IRS1/IRS1, p-PI3K/PI3K, and p-AKT/AKT proteins, while the levels of p-FoxO1/FoxO1 were significantly reduced compared to the model group ($p < 0.05$), thereby enhancing insulin signalling and intracellular glucose transport, ultimately alleviating IR. This suggests that syringin can enhance insulin signalling pathway transmission in HepG2 cells under IR conditions.

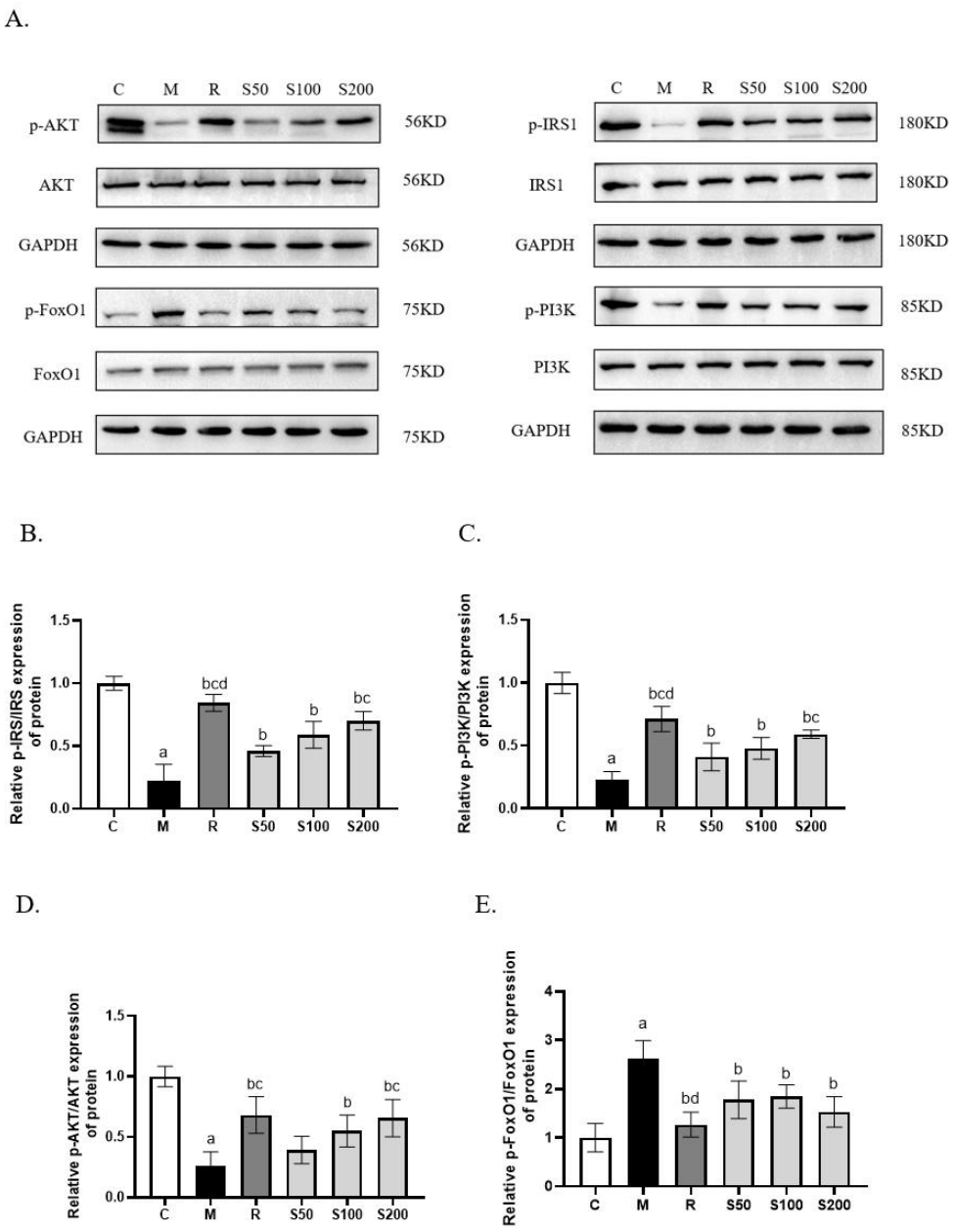

Fig. 6. Relative expression levels of IRS-1, PI3K, AKT, and FoxO1 proteins in HepG2 cells after syringin intervention. (A) Immunoblots showing the contents of for p-IRS1, IRS1, p-PI3K, PI3K, p-AKT, AKT, p-FoxO1, FoxO1, and the internal control GAPDH. (B, C, D, E) Relative protein levels of p-IRS1/IRS1, p-PI3K/PI3K, p-AKT/AKT, and p-FoxO1/FoxO1 in C, M, R, S50, S100 and S200 (means ± SD). a – $p < 0.01$, compared to the control group; b – $p < 0.05$, compared to the model group; c – $p < 0.05$, compared to the S50 group; C – control; M – model; R – rosiglitazone; S50 – syringin 50 μg mL^{-1}; S100 – syringin 100 μg mL^{-1}; S200 – syringin 200 μg mL^{-1}.

CONCLUSIONS

In summary, our findings indicate that syringin improves IR through multiple mechanisms, including the regulation of intracellular glucose and TG levels, modulation of immune factor levels, and activation of insulin signalling pathways. These results provide a strong foundation for considering syringin as a potential therapeutic for metabolic diseases. However, this study did not include animal experiments to evaluate the effects of syringin *in vivo*, which may constrain a comprehensive understanding of its systemic mechanisms. Therefore, future research should expand the sample size and include animal studies to more thoroughly evaluate the pharmacological effects of syringin.

Acronyms, abbreviations, symbols. – FOXO1 – fork head box protein O1, GRP78 – glucose-regulated protein 78, IL-6 – Interleukin-6, IR – insulin resistance，IRS1 – intracellular insulin receptor substrate 1, p-FoxO1 – phosphorylated-fork head box protein O1, PI3K—phosphatidylinositol 3-kinase, PPARγ – peroxisome proliferator-activated receptor gamma, p-PI3K – phosphorylated-phosphatidylinositol 3-kinase, RSG – rosiglitazone, T2DM – type 2 diabetes, TG – triglyceride, TNF-α – tumour necrosis factor alpha.

Data availability statement. – The publication and its supplemental materials contain the original contributions described in this research. The corresponding author can be contacted with any further enquiries.

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Conflict of interest. – The authors report no potential conflicts of interest.

Author's contribution. – Conceptualization, H.W.; methodology, H.W., J.H., and X.W.; analysis, L.Y.; writing, original draft preparation, H.W.; writing, review and editing, H.W., J.H., L.Y., and X.W. All authors have read and agreed to the published version of the manuscript.

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