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Influence and treatment of insulin receptor substrate/PI3K/Akt-mediated insulin resistance in diabetes mellitus (Review)

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Abstract. Diabetes is a metabolic disorder that has notable impacts on human health. Since improving insulin sensitivity and metabolic homeostasis is important for the treatment of diabetes and its complications, there is a need to evaluate therapies that improve insulin resistance. The aim of the present review was to introduce the effects of the insulin receptor substrate (IRS)/PI3K/Akt pathway on insulin resistance by summarizing and evaluating all existing insulin signaling pathway studies as the entry point, and to integrate the processes and mechanisms through which drugs alleviate insulin resistance. Peer-reviewed studies and reports on diabetes, insulin resistance and drug therapy were retrieved by searching websites such as PubMed (https://pubmed.ncbi.nlm.nih.gov/) and China National Knowledge Infrastructure (CNKI, https://www.cnki.net/), as well as by a manual search. The present review discusses the association between diabetes and the IRS/PI3K/Akt pathway, the treatment of diabetes by regulating this pathway to alleviate insulin resistance, the process and mechanism of combining drugs to alleviate insulin resistance, including natural compounds, Traditional Chinese Medicine and active ingredients, and the latest modern treatment methods. In conclusion, the present review summarizes the potential role of the IRS/PI3K/Akt pathway in the treatment of diabetes through its effect on insulin resistance and elucidates the therapeutic effects of drugs targeting this pathway.

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Key words: diabetes mellitus, insulin receptor substrate/PI3K/Akt, signal transduction, insulin resistance

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1. Introduction

Diabetes mellitus is a metabolic disease characterized by persistent hyperglycemia. Type 2 diabetes mellitus (T2DM) accounts for ~90% of all cases of diabetes. In the disease process, due to impaired insulin sensitivity, the body's uptake and utilization of glucose are blocked, which leads to the clinicopathological diagnosis characterized by glucose intolerance (1). At present, research on the pathogenesis of diabetes continues to advance, and insulin resistance has been found to be the main feature and pathogenic factor of T2DM (2). The insulin receptor (IR) substrate (IRS)/PI3K/Akt pathway is the classical insulin metabolic pathway (3). Glucose transporter type 2 (GLUT2) is constitutively expressed in the liver and pancreatic β cells, and its transport activity is predominantly driven by a glucose concentration gradient. In its physiological state, hepatic GLUT2 maintains glucose homeostasis through bidirectional transport (4). In the early stage of insulin resistance, where the IRS-1/PI3K/Akt pathway is not completely inactivated, Akt may inhibit glycogen synthesis by phosphorylating glycogen synthase kinase 3β (GSK3β) and indirectly enhance GLUT2-mediated gluconeogenesis (5). GLUT2 activity is predominantly driven by concentration gradients for glucose transport in tissues such as the liver, independent of insulin stimulation. However, membrane translocation of GLUT4 in muscle and adipose tissue is strictly dependent on insulin signaling. After PI3K is activated by tyrosine phosphorylation of IRS-1, phosphatidylinositol 3,4,5-triphosphate (PIP3) is generated to recruit 3-phosphoinositide-dependent protein kinase 1 and activate Akt (6). Activated Akt promotes the fusion of GLUT4 vesicles to the cell membrane by phosphorylating TBC1 domain family member 4 (AS160) (7). Serine phosphorylation of IRS-1, such as at Ser307, inhibits tyrosine phosphorylation in insulin resistance, leading to the blockade of the PI3K/PIP3/Akt pathway and reduced GLUT4 translocation (8).

Insulin regulates glucose uptake and metabolism in insulin-dependent tissues, such as muscle and fat, by activating specific signaling pathways and inducing GLUT4 transport, thereby maintaining the blood glucose balance (9). By regulating the IRS/PI3K/Akt signaling pathway, gluconeogenesis can be reduced, liver glycogen synthesis can be promoted, insulin resistance can be reduced and blood glucose levels in the body can be restored to normal (10).

2. IRS/PI3K/Akt signaling

The insulin-related signaling pathway is the molecular basis for the regulation of insulin metabolism, and the IRS/PI3K/Akt signaling pathway serves a key role in improving glucose metabolism and conversion *in vivo* (11). Its mechanism of action is that islet β cells secrete insulin, which binds to corresponding receptors on target cells and serves a role in lowering blood glucose *in vivo*. IR, a member of the tyrosine kinase family, is a tetrameric protein structure composed of two α subunits and two β subunits. When insulin is not bound to its receptor, the tyrosine kinase in the cell dissociates, forms a λ type and the kinase activity is autoinhibited (12). When insulin binds to the α subunit of IR on the target cell, the protein conformation changes, the β subunit is activated and some tyrosine residues within the cell are autophosphorylated, and these are subsequently recognized and recruited by the phosphotyrosine binding domain of the adaptor protein. Blocking of insulin signaling leads to insulin resistance and metabolic system disorders (13).

As blood glucose levels continue to rise in the body, insulin binds to the IR on the cell surface and autophosphorylates downstream IRS proteins (14). IRS-1 was the first identified IR substrate, and is widely expressed in a variety of tissues, such as muscle and adipose tissue, and cell types. IRS-1 is one of the key molecules mediating insulin and insulin-like growth factor-1 signaling (15). Following insulin-IR binding, IRS-1 is subsequently recruited and phosphorylated, and specific tyrosine residues on phosphorylated IRS-1 provide binding sites for the p85 regulatory subunit of PI3K, through which PI3K is activated (16,17). IRS-2 is abundantly expressed in the liver, islet β cells, adipose tissue and other tissues. IRS-2 serves an important role in regulating glucose metabolism in the liver, and the survival and function of islet β cells. Similar to IRS-1, insulin signaling activates the IR and phosphorylates IRS-2 to bind to the p85 subunit of PI3K. In addition, IRS-2 activates PI3K and its downstream signaling pathways (18-20). IRS-3 is predominantly expressed in adipose tissue and the liver, while IRS-4 is expressed in endocrine glands, such as the pituitary, thyroid and adrenal glands, and some tumor cells. Following its activation by the corresponding receptors, IRS-4 can recruit the p85 subunit of PI3K by phosphorylation to activate PI3K, and participate in the regulation of cell growth, proliferation and metabolism (21). Tyrosyl-phosphorylated IRS proteins bind to the Src homology 2 domain signaling molecule of the PI3K regulatory subunit p85 and recruit the catalytic subunit p110 of PI3K to activate PI3K. Tyrosyl-phosphorylated IRS binds to downstream PI3K in activated cells and promotes PI3K activation (22).

PI3K is a downstream effector of IRS. Upon binding to IRS proteins phosphorylated by tyrosine, PI3K activates phosphatidylinositol phosphorylation to generate PIP3, which in turn activates the serine/threonine protein kinase Akt (23). Akt activates a variety of substrates and mediates a variety of insulin-acting organisms, thereby promoting glucose transporters in the cell membrane to accelerate glucose uptake and utilization, a process important for maintaining a normal glycemic range (24). A key role of insulin in maintaining blood glucose is to induce the translocation of GLUT4 from intracellular storage sites to the plasma membrane, which promotes glucose uptake by cells and reduces insulin resistance (25) (Fig. 1).

3. Effects of the IRS/PI3K/Akt pathway on insulin resistance

Insulin resistance is an important factor in the development of diabetes and is characterized by a reduced ability of insulin to promote tissue glucose uptake and utilization (26). Impaired IRS signaling induces and exacerbates insulin resistance. Previous studies have shown that glucose metabolism is predominantly manifested in target tissues through the IRS-1/PI3K/Akt pathway, which is an important signaling pathways that regulates the blood glucose balance through insulin (27,28). With the development of diabetes research, the importance of the IRS/PI3K/Akt signaling pathway in insulin resistance has been gradually realized. Abnormal activation of this pathway leads to the weakened response of liver, muscle and other tissues to insulin, so that blood glucose levels cannot be effectively controlled (29). The regulation of this pathway can effectively alleviate insulin resistance and provide novel ideas for the treatment of diabetes.

The liver serves an important role in glucose metabolism; when the body exhibits insufficient insulin secretion, the liver produces excessive glucose, which disrupts the balance of peripheral glucose consumption and leads to continuous blood glucose elevation (30). Hepatic insulin resistance is an important pathological feature of T2DM (31). Under physiological conditions, the initial step for insulin to exert its biological effects is its specific binding to the IR on the surface of target cells. This binding triggers conformational changes and autophosphorylation activation, thereby initiating a downstream signal transduction cascade. IRS-1, as a key downstream adaptor molecule, can bind to the intracellular domain phosphorylated by the activated IR through its specific domain, thereby completing insulin signaling (32). By activating PI3K and its downstream target Akt, glucose metabolism disorders in the liver can be directly improved, and thus, it also plays a role in the intervention of insulin resistance (33). The stimulation of the PI3K/Akt signaling pathway promotes glucose uptake and activates GSK3β, thereby promoting glycogen synthesis (34). Previous studies have shown that some natural drug extracts or fractions

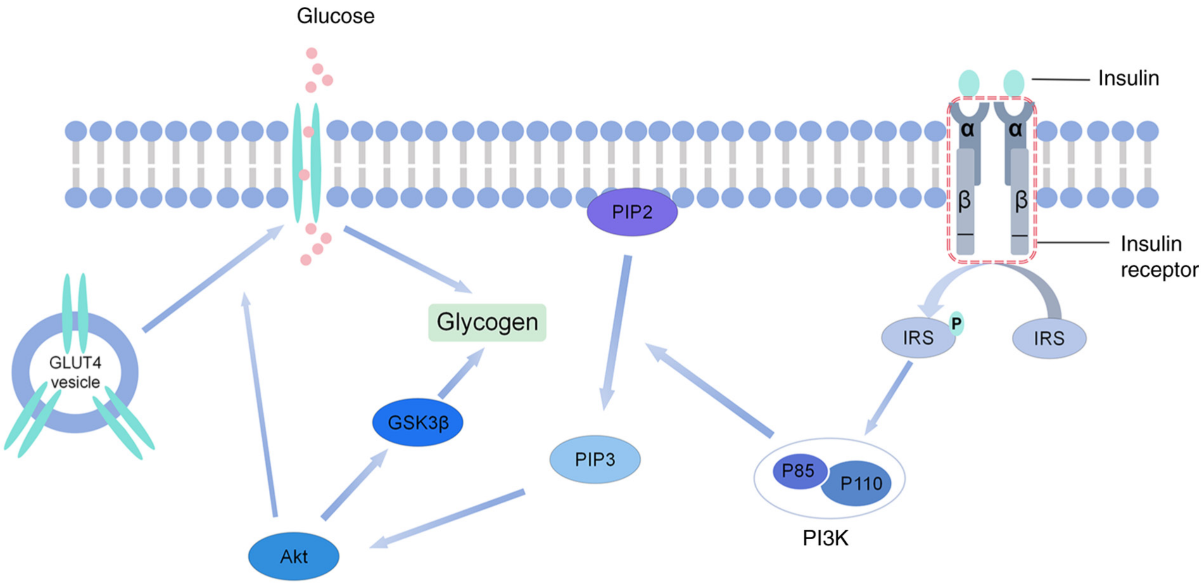

Figure 1. Flow chart of the mechanism of the IRS/PI3K/Akt signaling pathway in diabetes-induced insulin resistance. IRS, insulin receptor substrate; GLUT4, glucose transporter type 4; GSK3, glycogen synthase kinase 3; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; P, phosphate group.

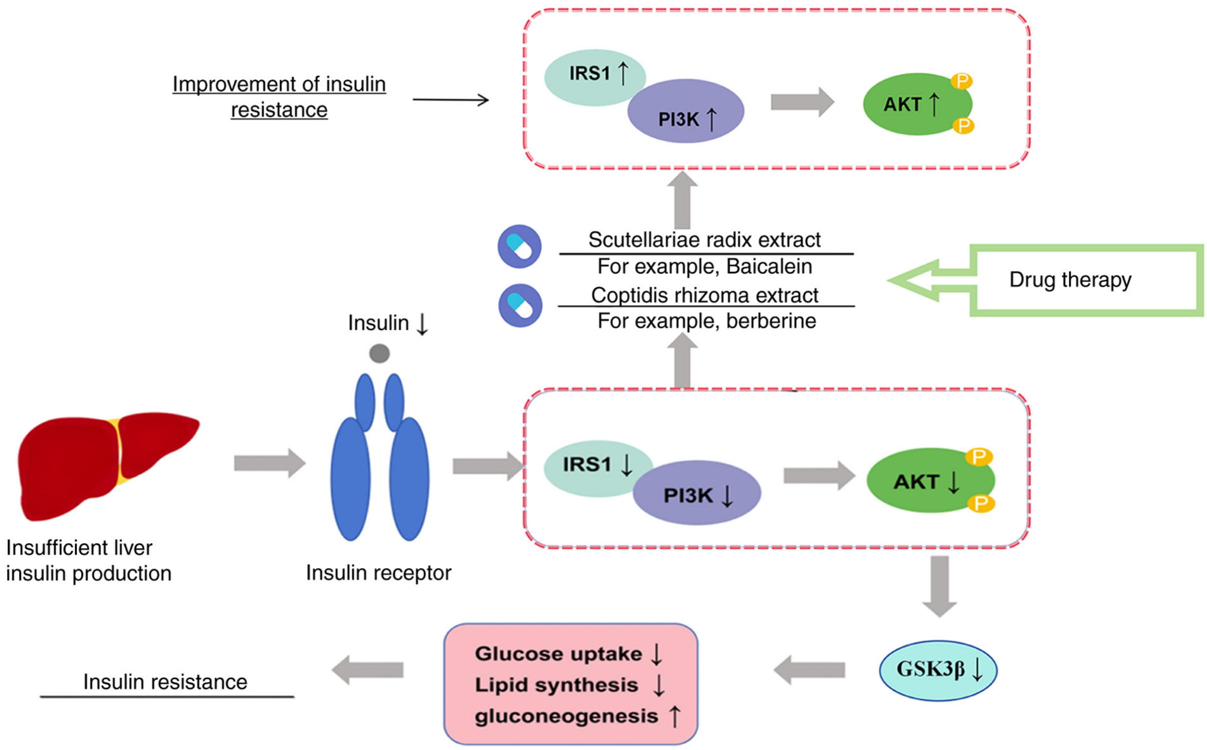

Figure 2. Effects of the IRS/PI3K/Akt pathway on hepatic insulin resistance. The mechanism of the IRS/PI3K/Akt pathway in insulin resistance and the therapeutic effect of drugs was explored in the pathogenesis of diabetes. IRS, insulin receptor substrate; GSK3β, glycogen synthase kinase 3β; P, phosphate group.

improve insulin resistance and reduce blood glucose levels by activating the IRS/PI3K/Akt pathway (35-37). Studies have found that natural medicinal plants and tea can also activate the PI3K/Akt signaling pathway and improve the sensitivity of skeletal muscle to insulin, thereby effectively reducing insulin resistance in diabetic mice (38-40). This opens up novel possibilities for the treatment of diabetes. In summary, the IRS/PI3K/Akt signaling pathway is one of the key signaling pathways in the pathogenesis of diabetes. By inhibiting the IRS/PI3K/Akt pathway and down-regulating GSK3β, it reduces glucose uptake and lipid synthesis, and increases gluconeogenesis, thereby causing insulin resistance. Drugs (such as Baicalein and berberine), by enhancing the activity of IRS-1/PI3K and promoting Akt phosphorylation, alleviate insulin resistance and play a crucial role in the pathogenesis of diabetes (41-43) (Fig. 2).

4. Interrelationship between the IRS/PI3K/Akt and AMP-activated protein kinase (AMPK) signaling pathways

In insulin resistance, there is a complex relationship between the IRS/PI3K/Akt and AMPK signaling pathways. These pathways affect and regulate each other and participate in the occurrence and development of insulin resistance (44). AMPK can regulate the IRS/PI3K/Akt pathway by phosphorylating IRS. When exercise or energy stress occurs, AMPK is activated, and this can phosphorylate certain serine residues on IRS-1. This phosphorylation affects the binding of IRS-1 to IR and its interaction with PI3K, which in turn regulates downstream signaling (45). In general, moderate AMPK activation causes the phosphorylation of AS160 at Thr642, which promotes the fusion of GLUT4 vesicles to the cell membrane. In addition, AMPK activates tuberin, inhibits mTOR complex 1, reduces the phosphorylation of ribosomal protein S6 kinase β-1 (S6K1) on IRS-1, decreases the negative feedback phosphorylation of S6K1 on IRS-1, and protects the integrity and signal transduction efficiency of the IRS/PI3K/Akt pathway. Activated Akt inhibits AMPK through phosphorylation, and this negative feedback regulation can prevent the excessive activation of AMPK and maintain the intracellular metabolic balance. However, when energy metabolism is abnormal, AMPK is overactivated to inhibit β cell stress and cell death, thereby promoting the occurrence and development of diabetes (46,47).

Insulin can also increase intracellular ATP levels by increasing intracellular glucose uptake and metabolism, thereby activating AMPK. The IRS/PI3K/Akt signaling pathway increases glucose uptake and utilization by cells by promoting GLUT4 translocation to the cell membrane, while promoting glycogen synthesis and inhibiting gluconeogenesis (48). AMPK also promotes glucose uptake through the activation of downstream 6-phosphofructose-2-kinase/fructose-2,6-biphosphatase 2, increasing glycolysis. AMPK also inhibits the expression of gluconeogenesis-related genes and reduces gluconeogenesis (49). The IRS/PI3K/Akt and AMPK signaling pathways work together to maintain the balance of glucose metabolism, and during insulin resistance, this synergy is dysregulated, leading to increased blood glucose levels.

5. Research progress regarding the IRS/PI3K/Akt pathway in the treatment of diabetes

The IRS/PI3K/Akt pathway is the key pathway of insulin signal transduction and serves a central role in the occurrence and development of insulin resistance. This article elaborates on how drugs can improve insulin resistance by regulating the IRS/PI3K/Akt pathway. The existing research has been summarized in the present review and can be used to help alleviate insulin resistance caused by diabetes by regulating the IRS/PI3K/Akt pathway.

Natural drug extracts. Some monomeric active ingredients in natural drug extracts have been found to improve glucose metabolism and insulin resistance by regulating the IRS/PI3K/Akt signaling pathway (Table I). It has been found that the abundance and diversity of gut microbiota are associated with the occurrence and development of diabetes. Diosmetin regulates *Corynebacterium glutamicum* through the IRS/PI3K/Akt signaling pathway, reduces the firmicute/bacteroidete ratio, notably increases the abundance of *Corynebacterium glutamicum* and alters the intestinal flora (50). In KK-Ay type diabetic mice, compared with that in the control group, the glucose metabolism of the mice treated with Diosmetin improved significantly (51). Astragaloside IV (AS-IV) could markedly reduce blood lipid and glucose levels, as well as insulin resistance and oxidative stress in T2DM model mice. AS-IV was also shown to protect the liver and pancreatic cell structure. High-throughput 16S ribosomal RNA gene sequencing was used to determine the composition of gut microbiota in the model mice. As a result, AS-IV was found to increase the levels of butyrate, and improve the abundance and diversity of intestinal flora in model mice. The mechanism by which AS-IV alleviates insulin resistance was linked to the regulation of the AMPK/sirtuin 1 (SIRT1) and PI3K/Akt signaling pathways (52).

3,3',4,5'-tetramethoxy-trans-stilbene (2.5 μM) can upregulate the phosphorylation of GSK3β^{Ser9}, inhibit the phosphorylation of IRS-1^{Ser307}, increase the levels of IRS-1 and IRS-2, activate the PI3K/Akt pathway and promote glycogen synthesis. It has been shown to reduce the oxidative stress level of HepG2 cells by upregulating nuclear factor erythroid 2-related factor 2, as well as to regulate insulin sensitivity and homeostasis, thus improving insulin resistance (53). *Anemarrhena* saponins have been shown to have lipid-lowering and glucose-lowering effects. In an experiment investigating the effect of treatment with *Anemarrhena* saponins in insulin-resistant rats, the phosphorylation levels of IRS-1, PI3K and Akt were increased in model rats compared with controls. The mRNA expression levels of glucose-6-phosphatase (G6pase), phosphoenolpyruvate carboxykinase (PEPCK) and GSK3β were notably decreased (54).

A study showed that guava leaves have anti-diabetic effects. After 8 weeks of treatment with guava leaf extract in KK-Ay diabetic mice, the body weight, fasting blood glucose, fasting insulin and insulin resistance index of diabetic model mice were markedly decreased, while the insulin sensitivity index was increased. The protein and gene expression levels of IRS-1, PI3K and Akt in the liver were also upregulated, suggesting that guava leaf extract could improve insulin resistance in KK-Ay diabetic mice by regulating the IRS/PI3K/Akt signaling pathway, and may serve a role in the treatment of diabetes (55).

Abnormal glucose and lipid metabolism are associated with insulin resistance and the development of T2DM (56). Impaired insulin function results in notable reductions in glucose uptake, glucose consumption and glycogen storage, as well as marked increases in plasma glucose levels (57). Oxidative stress can disrupt normal insulin signaling, and increase the risk of insulin resistance, glucose and lipid metabolism disorders, and diabetes (58). Flavonoids from *Potentilla bifurca* can effectively improve insulin resistance. Experiments have shown that this flavonoid component enhanced glucose uptake in adipocytes from the 3T3-L1 cell line. Insulin resistance can be improved by regulating the content of p-Akt/Akt, IKKβ and p-NF-κBp65/NF-κBp65 in the IRS/PI3K/Akt signaling pathway (59).

Table I. Research on the regulation of the insulin receptor substrate/PI3K/Akt signaling pathway by natural drug extracts and its role in improving insulin resistance.

First author/s, year	Medicine	*In vitro*/ *in vivo*	Experimental subject	Dosages	Remarks	(Refs.)
Gong *et al*, 2021	Diosmetin	*In vivo*	KK-Ay mice	20 and 60 mg/kg	Reshaped the imbalanced intestinal flora and improve glucose metabolism.	(51)
Gong *et al*, 2023	Astragaloside IV	*In vivo*	T2DM mice	25, 50 and 100 mg/kg	Improved the abnormal levels of blood lipids, blood glucose, insulin resistance and oxidative stress in T2DM mice.	(52)
Gong *et al*, 2023	Astragaloside IV	*In vitro*	HepG2 cells	12.5, 25 and 50 μM	By regulating the AMPK/SIRT1 and PI3K/AKT signaling pathways, oxidative stress and insulin resistance can be improved.	(52)
Tan *et al*, 2022	3,3',4,5'-tetramethoxy-trans-stilbene	*In vitro*	HepG2 cells	2.5 μM	Increased glucose consumption and glycogen synthesis and upregulated the antioxidant activity of nuclear factor erythroid 2-related factor 2.	(53)
Feng *et al*, 2021	*Anemarrhena* saponins	*In vivo*	Insulin-resistant Sprague-Dawley rats	100, 200 and 400 mg/kg	Promoted insulin signal transduction and alleviated liver damage caused by insulin resistance.	(54)
Yang *et al*, 2020	Guava leaf extract	*In vivo*	KK-Ay mice	1,638 mg/kg	Improved insulin resistance in KK-Ay diabetic mice and exerted an anti-diabetic effect.	(55)
Wang *et al*, 2022	*Potentilla bifurca* flavonoids	*In vitro*	3T3-L1 adipocytes	-	Improved the disorder of glycolipid metabolism in 3T3-L1 adipocytes and improved insulin resistance.	(59)

T2DM, type 2 diabetes mellitus.

Traditional medicine. T2DM is a metabolic disease characterized by hyperglycemia, with insulin resistance representing the leading cause (60). 1-deoxynojirimycin, an inhibitor of intestinal α-glucosidase, can effectively inhibit the conversion of glucose in the human body and is superior to the α-glucosidase inhibitor acarbose in terms of absorption (61). The glucose and insulin tolerance of db/db mice were improved following a 4-week course of intravenous injections with 1-deoxynojirimycin. This inhibitor also enhanced GLUT4 translocation, and phosphorylation of Ser473-Akt, p85-PI3K, Tyr1361-IR-β and Tyr612-IRS-1 in the skeletal muscle of db/db mice, suggesting that 1-deoxynojirimycin enhances insulin sensitivity through the IRS-1/PI3K/Akt pathway and increases the translocation of GLUT4 to the membrane, leading to an increase in muscle glycogen content (62,63). Metformin is commonly used in patients with diabetes. Metformin improves insulin sensitivity, inhibits glycogenolysis, reduces hepatic sugar output and does not result in notable weight gain (64). Metformin can alleviate T2DM-induced liver dysfunction and improve hepatic insulin resistance in T2DM model animals through the γ-aminobutyric acid type A receptor-independent PI3K/Akt/GLUT4 signaling pathway (65).

Rosiglitazone (RSG), a classical insulin sensitizer, improves lipid and glucose metabolism by activating peroxisome proliferator-activated receptor γ (PPARγ). Combined treatment with ursolic acid and RSG has been found to stimulate the translocation of IRS-1, PI3K, Akt and GLUT4. The IRS-1/PI3K/Akt-dependent signaling pathway can induce GLUT4 translocation and increase IR expression, thereby improving the induced glucose intolerance and insulin resistance (66). The glucagon-like peptide agonist liraglutide, which reduces blood glucose levels in patients with T2DM, has been found to reverse insulin resistance in skeletal muscle cells treated with palmitic acid (PA). The insulin-stimulated decrease in the level of glucose transporter 4 (GLUT4) on the cell surface caused by PA, as well as the phosphorylation phenomena of Akt, p85α-PI3K and AS160, all these effects of PA can be reversed after treatment with liraglutide. This indicates that liraglutide enhances insulin-induced GLUT4 translocation by inhibiting the serine phosphorylation of IRS-1 in muscle cells treated with PA (67).

Pioglitazone, a PPARγ agonist, can reduce insulin resistance in peripheral tissues and the liver, improve insulin sensitivity in patients with insulin resistance, enhance insulin responsiveness in cells and improve glucose balance disorders in the body. The activation of SIRT1 or PPARγ can alleviate abnormal glucose metabolism and decrease the protein expression of surfactant protein (SP)-B and SP-C in neonatal rats. SIRT1 enhances the expression of PPARγ by upregulating QKI5 and activates the PI3K/AKT pathway, thereby alleviating insulin resistance in late preterm rats (68). Adrenomedullin (ADM), an endogenous active peptide, is considered to be an adipokine involved in adipocyte function. PA induces the impairment of the insulin signaling pathway by affecting the PI3K/Akt axis and GLUT4 levels. ADM has been shown to reverse the effect of PA on the insulin signaling pathway, decrease the levels of pro-inflammatory factors TNF-α, IL-1β and IL-6, and alleviate oxidative stress (69). A summary can be found in Table II.

Modern methods of treatment. Vascular endothelial growth factor B (VEGFB) is a member of the vascular endothelial growth factor family and plays a role in the balance of glucose and lipid metabolism (70). Experiments have demonstrated that VEGFB/VEGFR1 activates PI3K/Akt signaling by increasing the levels of phosphorylated-IRS-1^{Ser307}, and inhibits the expression of phosphorylated-forkhead box $O1^{pS256}$ and phosphorylated-$GSK3^{Ser9}$, thereby reducing gluconeogenesis and glycogen synthesis in the liver (71). RSG is a traditional drug that alleviates insulin resistance, but its clinical application is limited due to the risk of adverse reactions. A co-crystal of RSG and berberine (RB) has been synthesized from RSG and RB at an molar ratio of 1:1 (72). RB was found to improve glucose and lipid metabolism, insulin resistance, and diabetes-induced liver and pancreatic lesions in high glucose and PA-stimulated KK-Ay mice, as well as in C2C12 and HepG2 cell lines. The upregulation of p-PI3K and p-Akt in KK-Ay mice, and HepG2 and C2C12 cells may be associated with regulation of the PI3K/Akt signaling pathway (73).

Tetrahedral framework nucleic acid is a DNA nanomaterial that has been shown to increase glucose uptake and improve insulin resistance via the IRS-1/PI3K/Akt pathway (74). Dysregulation of negative regulators of insulin signaling, such as PTEN, induces insulin resistance through a mechanism associated with hyperactivation (75). It has been found that human umbilical cord mesenchymal stem cells (HUC-MSCs) can effectively control the development of diabetes by restoring islet function and improving insulin resistance (76). This may be associated with PTEN regulating the PI3K/Akt pathway and reducing inflammatory release. HUC-MSCs stimulate glucose uptake and improve insulin action; melatonin increases the proliferation, migration and differentiation of HUC-MSCs by regulating the PI3K/Akt signaling pathway, thereby alleviating impaired glucose control and insulin resistance (77).

MicroRNA (miR)-27a has been shown to be involved in the signaling pathways associated with glucose metabolism in insulin resistance. PPARγ is the direct target of miR-27a, and has been shown to improve insulin resistance and mediate glucose metabolism. The mechanism of miR-27a activity is associated with regulation of the PPARγ-PI3K/Akt-GLUT4 signaling axis (78). It has also been confirmed that miR-506-3p expression is associated with insulin sensitivity and regulates the expression of S6K1, which participates in the protein expression of key genes in the PI3K/Akt insulin signaling pathway and alleviates insulin resistance in adipocytes, by binding to its 3' untranslated region (79). The RNA-binding protein Grb10-interacting GYF protein 2 has been shown to mediate obesity-induced insulin resistance by upregulating double-stranded RNA-binding protein Staufen homolog 1/PTEN and disrupting the PI3K/Akt signaling axis (80). A summary can be found in Table III.

Other. Notably, certain components of everyday foods have also been found to alleviate insulin resistance. Tomato pectin, a potential active ingredient in tomato processing residues, can reduce insulin resistance and inflammatory factor expression in the liver of model mice by regulating the PI3K/Akt pathway (81). Consumption of dietary chokeberry and dried jujube alters the protein expression of IRS, PI3K, Akt and catalase in the liver, all of which have been implicated in insulin resistance (82). Theabrownin is a bioactive component in dark tea that regulates glucose and lipid metabolism. Theabrownin has been shown to reverse insulin resistance in HepG2 cells through the IRS/PI3K/Akt signaling pathway, to regulate GSK3β, G6Pase, glucokinase, PEPCK1 and other related indicators, reduce oxidative stress (83). Pterostilbene effectively rescues advanced glycation end-product (AGE)-induced phenotypes and enhances IRS-1/PI3K/Akt insulin signaling in a dose-dependent manner in both Lo2 and HepG2 cell lines. The results of animal experiments are consistent with *in vitro* results, revealing a reduction of AGE accumulation in the liver and serum (84). Vitamin D deficiency can also cause insulin resistance; however, vitamin D supplementation cannot markedly mediate the increase of acute inflammation and insulin resistance in obesity (85).

6. Discussion

Insulin resistance is a key pathological feature affecting the development of T2DM. Therefore, effective control of insulin resistance is important for the prevention and treatment of diabetes (86). The insulin-related signaling pathway is the molecular basis of insulin regulation of metabolism. The binding of insulin to its receptor activates the PI3K/Akt pathway, thereby improving glucose metabolic transformation, including glucose uptake and glycogenesis (87).

In the field of diabetic insulin resistance research, further research on the IRS/PI3K/Akt signaling pathway needs to address the following issues. The core flaws can be summarized as two major research gaps: i) Focusing on the basic regulatory mechanism of the IRS/PI3K/Akt signaling pathway in insulin resistance during diabetes; or ii) only focusing on the research progress of a single treatment method, such as the use of natural drugs alone or traditional treatment regimens.

Table II. Research on the regulation of the IRS/PI3K/Akt signaling pathway by traditional drugs to improve insulin resistance.

First author/s, year	Medicine	*In vitro*/ *in vivo*	Experimental subject	Dosages	Remarks	(Refs.)
Liu *et al*, 2015	1-deoxynojirimycin	*In vivo*	db/db mice	20, 40 and 80 mg/kg	By activating the insulin signaling PI3K/AKT pathway in the skeletal muscles of db/db mice, insulin sensitivity was significantly enhanced.	(62)
Kang *et al*, 2022	1-deoxynojirimycin	*In vivo*	db/db mice	40 mM/kg	Regulated the insulin signaling pathway in the skeletal muscle of db/db mice to improve insulin resistance.	(63)
Garabadu and Krishnamurthy, 2017	Metformin	*In vivo*	Type 2 diabetes mellitus rats	25 mg/kg	Alleviated the diabetes-induced reduction of phosphorylated Akt and GLUT4 translocation in the liver and improved insulin resistance.	(65)
Sundaresan *et al*, 2016	Ursolic acid and rosiglitazone	*In vivo*	C57/BL/6J mice	Ursolic acid (5 mg/kg); rosiglitazone (4 mg/kg)	Increased the expression of insulin receptors and improved high fat diet-induced glucose intolerance and insulin resistance.	(66)
Li *et al*, 2018	Liraglutide	*In vitro*	C2C12-GLUT4 myc-tagged cells	100 nM	Inhibited the phosphorylation of IRS-1 serine in muscle cells treated with PA to enhance insulin-induced GLUT4 translocation.	(67)
He *et al*, 2023	Pioglitazone	*In vivo*	Wistar rats	5 mg/kg	Upregulation of quaking-5 promoted the expression of peroxisome proliferator-activated receptor γ, activated the PI3K/Akt pathway and improved insulin resistance.	(68)
He *et al*, 2023	Pioglitazone	*In vitro*	AT-II cells	100 nM	Activation of SIRT1 alleviates abnormal glucose metabolism, reduces the expression of SP-B and SP-C, activates the PI3K/AKT pathway, and decreases cellular inflammation and apoptosis.	(68)
Dai *et al*, 2022	Adrenomedullin	*In vivo*	Obese rats	300 ng/kg	Improved insulin resistance in obese rats, restored insulin signal transduction and reduced inflammation and oxidative stress.	(69)
Dai *et al*, 2022	Adrenomedullin	*In vitro*	3T3-L1 adipocytes	10 nM	Regulating the PI3K/Akt pathway improved insulin resistance, inflammation and oxidative stress induced by PA in adipocytes.	(69)

AT-II, alveolar type II; IRS, insulin receptor substrate; GLUT, glucose transporter.

Table III. Research on the improvement of insulin resistance by modern technology regulating the insulin receptor substrate/PI3K/Akt signaling pathway.

First author/s, year	Modern technology	*In vitro*/ *in vivo*	Experimental subject	Dosages	Remarks	(Refs.)
Li *et al*, 2024	VEGFB gene	*In vivo*	VEGFB knockout mice	-	Activate the PI3K/AKT signaling pathway in mice, inhibit glucose production and promote glycogen synthesis, thereby improving insulin resistance and hepatic steatosis.	(71)
Li *et al*, 2024	VEGFB gene	*In vitro*	HepG2 cells	-	Activate the PI3K/AKT signaling pathway in HepG2 cells induced by PA, and improve the levels of glucose and lipids.	(71)
He *et al*, 2022	Co-crystal of rosiglitazone with berberine	*In vivo*	KK-Ay mice	0.7, 2.11 and 6.33 mg/kg	The mechanism of improving insulin resistance and metabolic disorders may involve regulation of thePI3K/Akt/thioredoxin-interacting protein signaling pathway.	(73)
Li *et al*, 2021	Tetrahedral framework nucleic acids	*In vitro*	HepG2 cells	-	Reduced blood glucose levels and improved insulin resistance in hepatocytes through the PI3K/Akt pathway.	(74)
Chen *et al*, 2020	HUC-MSCs	*In vivo*	db/db mice	1×10^7 HUC-MSCs (in 0.7 ml saline) or 1×10^8 HUC-MSCs (in 2 ml aline)	By regulating the PI3K/Akt and ERK/MAPK signaling pathways through PTEN, insulin resistance is alleviated.	(76)
Aierken *et al*, 2022	Melatonin and HUC-MSCs	*In vivo*	Kunming mice	1×10^6 HUC-MSCs (in 0.2 ml of 0.9% NaCl)	Regulating the PI3K/AKT pathway leads to hUC-MSC stimulating glucose uptake and improving insulin action.	(77)
Chen *et al*, 2019	AD-miR-27a	*In vivo*	Obese mice	1.0×10^8 plaque-forming units (in 0.2 ml PBS)	miR-27a was involved in the PPARγ-PI3K/Akt-GLUT4 signaling axis, increasing glucose uptake and reducing insulin resistance.	(78)
Chen *et al*, 2019	AD-miR-27a	*In vitro*	3T3-L1 adipocytes	10 nM	MiR-27a activates through PPAR-γ and activates the PI3K/Akt signaling pathway to regulate insulin sensitivity.	(78)
Zhong *et al*, 2021	miR-506-3p mimic	*In vitro*	Human preadipocytes	-	Insulin resistance of adipocytes was altered by regulating the activation of the ribosomal protein S6kinase β-1-mediated PI3K/Akt pathway.	(79)
Lv *et al*, 2024	RNA-binding protein GIGYF2	*In vivo*	C57BL/6J mice	1×10^9 plaque-forming units/100 μl (GIGYF2 lentivirus)	GIGYF2 disrupted the PI3K/Akt signaling axis by upregulating double- stranded RNA-binding protein staufen homolog 1/PTEN, thereby mediating obesity-related insulin resistance.	(80)

Table III. Continued.

First author/s, year	Modern technology	*In vitro*/ *in vivo*	Experimental subject	Dosages	Remarks	(Refs.)
Lv *et al*, 2024	RNA-binding protein GIGYF2	*In vitro*	HepG2 and 293T cells	-	GIGYF2 promotes insulin resistance through PTEN-mediated inactivation of the PI3K/AKT pathway in hepatocytes.	(80)

HUC-MSC, human umbilical cord mesenchymal stem cell; miR, microRNA; GIGYF2, Grb10-interacting GYF protein 2; AD-miR-27a, adenovirus expressing miR-27a; GLUT, glucose transporter; VEGFB, vascular endothelial growth factor B; PPARγ, peroxisome proliferator-activated receptor γ.

The core flaws are manifested in two aspects: i) There is a disconnect between mechanism explanation and treatment application, failing to establish a connection between the basic mechanism and clinical intervention; and ii) there remain only sporadic mentions of the abnormality of a single molecule, such as IRS-1 or Akt, and its influence on insulin resistance, without systematically sorting out the abnormal interaction patterns among molecules within the pathway, leaving research gaps. These two aspects are mutually related and jointly restrict the breakthrough from basic mechanism elucidation to clinical translation in this field.

Since insulin resistance plays an important role in the pathogenesis of diabetes, and IRS/PI3K/Akt signaling pathway is an important pathway of insulin resistance, this review elaborates the relationship between IRS and PI3K/Akt, and explores the role of IRS/PI3K/Akt in insulin resistance in general. The regulatory value and importance of insulin resistance in the early stage of diabetes are reviewed. Primarily, the present review clarified the cascade effect of IRS phosphorylation imbalance leading to PI3K activation blockage, which in turn results in Akt signal silencing in the insulin signaling pathway under pathological conditions, and its core driving role in the occurrence and development of insulin resistance. For example, an increase in Ser307 phosphorylation of IRS-1 will prevent the p85 subunit of PI3K from binding, thereby reducing the phosphorylation level of Thr308 or Ser473 in Akt and ultimately inhibiting the membrane translocation of GLUT4 and the activation of glycogen synthase (88). Furthermore, the present review simultaneously clarified how targeted intervention against this cascade effect, such as regulating the balance of serine phosphorylation of insulin receptor molecules, drug co-crystallization technology and tetrahedral framework nucleic acid nanomaterials, can directly promote glucose transport by increasing the expression level of GLUT4 in the cell membrane, accelerate glycogen synthesis and maintain the lipid metabolism balance (89). In summary, the present review outlined how the IRS/PI3K/Akt pathway is the key intervention target for improving insulin resistance in diabetes.

Drug therapy can improve insulin resistance by upregulating IRS-1, activating the PI3K/Akt pathway, promoting glycogen synthesis, and regulating glucose and lipid metabolism (90). Furthermore, drug therapies reduce oxidative stress and inflammation, increase the insulin sensitivity index, increase glucose uptake, glucose consumption and glycogen storage, decrease plasma glucose levels (91,92). These therapies include the isolation of active ingredients from natural medicines and research involves the establishment of animal or cell models to discover the effectiveness of extracts that serve a role in the treatment of T2DM (93-96). Traditional drugs and monomeric active ingredients can alleviate the inflammatory response, improve hepatic insulin resistance, and enhance glucose uptake and utilization in peripheral tissues by regulating the IRS/PI3K/Akt pathway, thereby improving abnormal lipid metabolism function and protecting islet β cells (97,98). Certain drugs have multi-target synergistic effects, which can not only regulate the IRS/PI3K/Akt and AMPK pathways, but also reduce the accumulation of AGEs and receptor for AGEs (99), upregulate IRS-1 and increase the phosphorylation of p85-PI3K and Akt, as well as improve related complications, such as polydipsia, polyphagia, polyuria and body wasting caused by diabetes (100).

The present review discusses how the intestinal microbiota of patients with T2DM not only show a higher concentration of flora, but are also structurally and functionally different from those of non-diabetic individuals. *Acidophilus*, *Blautia, Desulfovibrio, Dorea* and *Faecalibacterium*, as well as agglomerates and anaerobic bacteria, have been found to be nominally associated with T2DM (101). Gut bacteria have been shown to be associated with insulin resistance and sensitivity, to exhibit a distinct carbohydrate metabolism signature and, in the case of insulin sensitivity-related bacteria, to ameliorate the phenotype of host insulin resistance in mouse models (102). However, the molecular mechanisms of how gut microbiota directly regulate the IRS/PI3K/Akt pathway, such as the short-chain fatty acid/G-protein coupled receptor 43/PI3K axis, remain to be fully elucidated, and human intervention studies are limited. At present, the clinical treatment mainly focuses on targeted therapy, which is superior to traditional drug therapy in terms of efficacy, safety and precision. Novel drug therapies use co-crystals formed by the non-covalent bond between one active pharmaceutical ingredient and another, or in some cases multiple co-crystal forming agents. Co-crystals have previously been used in the field of medicine and show great potential in the treatment of type 2 diabetes, with co-crystal formation overcoming the adverse physicochemical properties of the parent drug by forming eutectic structures (72,73). Tetrahedral frame nucleic acids improve hepatic insulin resistance and alleviate type 2 diabetes (74). These novel technologies are of notable value in the treatment of diabetes. Furthermore, HUC-MSCs can restore the function of insulin. Melatonin can increase the proliferation, migration and differentiation of HUC-MSCs by regulating the PI3K/Akt signaling pathway, thereby controlling blood glucose levels and alleviating insulin resistance (76). However, there are few studies on the effect of stem cells on insulin resistance, which will have notable value in the future treatment of diabetes.

At present, the study of the IRS/PI3K/Akt pathway in insulin resistance still faces a number of challenges. The traditional view was that the IRS-1/PI3K/Akt pathway is inhibited when insulin resistance occurs, but this pathway is abnormally activated in specific tissues or stages (103). For example, although serine phosphorylation of IRS-1 in the liver inhibits PI3K activity, Akt may be activated through PI3K-independent pathways such as the RAS/MAPK pathway, leading to the upregulation of gluconeogenic genes (104). This partial activation is associated with tissue-specific regulation. Furthermore, studies predominantly focus on liver and adipose tissue, while the mechanistic analysis of skeletal muscle is relatively weak (105-107). Studies on different organizations should receive more attention in future research. In addition, the role of the p110α and p110β isoforms of PI3K in insulin resistance remains controversial. p110α serves a dominant role in hepatic glucose metabolism, while p110β may affect muscle insulin sensitivity by regulating GLUT4 transport (108,109). However, the majority of existing studies use pan-PI3K inhibitors such as LY294002, which leads to the masking of subtype-specific mechanisms (110).

In addition, due to insulin resistance being a progressive disease, the majority of studies use cross-sectional designs in animal experiments. For example, in the study on obesity and insulin resistance caused by high-fat diet (HFD), it was found that after 3 days of feeding with HFD, the phosphorylation of AMPK significantly decreased compared to mice fed with regular diet. After 14 days of feeding with HFD, systemic insulin resistance occurred, and the phosphorylation of Akt significantly decreased (111). This dynamic change suggests that there is a key point in pathway regulation, but existing models lack time series analysis. Furthermore, the translational dilemma between animal models and human studies is that the HFD-induced mouse model of insulin resistance shows a decreased expression of IRS-1 (112); however, in humans, a study focused on obese individuals without diabetes. Through skeletal muscle biopsy, it was found that the total protein level of IRS-1 in the skeletal muscles of obese individuals did not show significant fluctuations. However, different dietary interventions would cause obvious abnormalities in the phosphorylation of Ser307. For example, in the high-fat and low-carbohydrate diet group, the phosphorylation of Ser307 significantly increased, while in the low-fat and high-carbohydrate diet group, it showed a decreasing trend (113). In addition, ADM causes insulin resistance by interfering with endothelial insulin signaling in mouse models (114), but clinical evidence for this mechanism in humans is insufficient, suggesting that interspecies pathway differences may be underestimated.

The IRS/PI3K/Akt pathway can provide novel strategies and methods for the treatment of diabetes. However, the regulatory mechanism of this pathway and existing problems in diabetes research require further study in order to provide an improved theoretical basis and novel drug targets for the prevention and treatment of diabetes.

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Authors' contributions

CG and SD made substantial contributions to conception, design and funding support. WT drafted the manuscript. HL and XL revised it critically for important intellectual content. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, *et al*: Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International diabetes federation diabetes atlas, 9th edition. Diabetes Res Clin Pract 157: 107843, 2019.
2. DeFronzo RA and Tripathy D: Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 32 (Suppl 2): S157-S163, 2009.
3. Karagözoğlu F, Şahin E, Melek Ş, Bediz Şahin S, Koca RH, Yüksel H and Güngören A: Effects of apilarnil on type 2 diabetes-induced IRS-1/PI3K/Akt mediated insulin resistance in male rats. ACS Omega 10: 25027-25038, 2025.
4. Hong S, Lee J, Choi SY, Park JH and Lee YG: Ginsenoside Rf improves glucose metabolism via the IRS/PI3K/Akt and PPARα/PGC1α signaling pathways in insulin-resistant AML12 cells. BMC Complement Med Ther 25: 340, 2025.
5. Wang Y, Zhang L, He M, Chen X, Pei L and Xi S: Cobalt exposure increases fasting plasma glucose by inhibiting hepatic glycogen synthesis and enhancing gluconeogenesis. J Hazard Mater 499: 140132, 2025.
6. Luo Z, Xu W, Yuan T, Shi C, Jin T, Chong Y, Ji J, Lin L, Xu J, Zhang Y, *et al*: Platycodon grandiflorus root extract activates hepatic PI3K/PIP3/Akt insulin signaling by enriching gut Akkermansia muciniphila in high fat diet fed mice. Phytomedicine 109: 154595, 2025.

7. Horii N, Hasegawa N, Fujie S, Uchida M and Iemitsu M: Resistance exercise-induced increase in muscle 5α-dihydrotestosterone contributes to the activation of muscle Akt/mTOR/p70S6K- and Akt/AS160/GLUT4-signaling pathways in type 2 diabetic rats. FASEB J 34: 11047-11057, 2020.
8. Li Q, Su J, Jin SJ, Wei W, Cong XD, Li XX and Xu M: Argirein alleviates vascular endothelial insulin resistance through suppressing the activation of Nox4-dependent O2- production in diabetic rats. Free Radic Biol Med 121: 169-179, 2018.
9. Chadt A and Al-Hasani H: Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. Pflugers Arch 472: 1273-1298, 2020.
10. Wang G, Liu Z, Liang D, Yu J, Wang T, Zhou F and Chen W: Aqueous extract of Polygonatum sibiricum ameliorates glucose and lipid metabolism via PI3K/AKT signaling pathway in high-fat diet and streptozotocin-induced diabetic mice. J Food Biochem 46: e14402, 2022.
11. Liu X, Cai S, Yi J and Chu C: Chinese sumac fruits (Rhus chinesis Mill.) alleviate type 2 diabetes in C57BL/6 mice through repairing islet cell functions, regulating IRS-1/PI3K/AKT pathways and promoting the entry of Nrf2 into the nucleus. Nutrients 15: 4080, 2023.
12. Escribano O, Beneit N, Rubio-Longás C, López-Pastor AR and Gómez-Hernández A: The role of insulin receptor isoforms in diabetes and its metabolic and vascular complications. J Diabetes Res 2017: 1403206, 2017.
13. Li J, Park J, Mayer JP, Webb KJ, Uchikawa E, Wu J, Liu S, Zhang X, Stowell MHB, Choi E and Bai XC: Synergistic activation of the insulin receptor via two distinct sites. Nat Struct Mol Biol 29: 357-368, 2022.
14. Yuan YL, Lin BQ, Zhang CF, Cui LL, Ruan SX, Yang ZL, Li F and Ji D: Timosaponin B-II ameliorates palmitate-induced insulin resistance and inflammation via IRS-1/PI3K/Akt and IKK/NF-[Formula: see text]B pathways. Am J Chin Med 44: 755-769, 2016.
15. Franko A, Kunze A, Böse M, von Kleist-Retzow JC, Paulsson M, Hartmann U and Wiesner RJ: Impaired insulin signaling is associated with hepatic mitochondrial dysfunction in IR+/-IRS-1+/- double heterozygous (IR-IRS1dh) mice. Int J Mol Sci 18: 1156, 2017.
16. Draznin B: Molecular mechanisms of insulin resistance: serine phosphorylation of insulin receptor substrate-1 and increased expression of p85alpha: The two sides of a coin. Diabetes 55: 2392-2397, 2006.
17. Krisnamurti DGB, Louisa M, Poerwaningsih EH, Tarigan TJE, Soetikno V, Wibowo H and Nugroho CMH: Vitamin D supplementation alleviates insulin resistance in prediabetic rats by modifying IRS-1 and PPARγ/NF-κB expressions. Front Endocrinol (Lausanne) 14: 1089298, 2023.
18. Granata R, Settanni F, Gallo D, Trovato L, Biancone L, Cantaluppi V, Nano R, Annunziata M, Campiglia P, Arnoletti E, *et al*: Obestatin promotes survival of pancreatic beta-cells and human islets and induces expression of genes involved in the regulation of beta-cell mass and function. Diabetes 57: 967-979, 2008.
19. Sharfi H and Eldar-Finkelman H: Sequential phosphorylation of insulin receptor substrate-2 by glycogen synthase kinase-3 and c-Jun NH2-terminal kinase plays a role in hepatic insulin signaling. Am J Physiol Endocrinol Metab 294: E307-E315, 2008.
20. Luo Q, Ling Z, Huang X and Zuo Y: Association of IRS-1 and IRS-2 polymorphisms with predisposition to type-2 diabetes (T2D): A meta-analysis and trial sequential analysis. Nucleosides Nucleotides Nucleic Acids 42: 837-851, 2023.
21. Escribano O, Fernández-Moreno MD, Zueco JA, Menor C, Fueyo J, Ropero RM, Diaz-Laviada I, Román ID and Guijarro LG: Insulin receptor substrate-4 signaling in quiescent rat hepatocytes and in regenerating rat liver. Hepatology 37: 1461-1469, 2003.
22. Boura-Halfon S and Zick Y: Phosphorylation of IRS proteins, insulin action, and insulin resistance. Am J Physiol Endocrinol Metab 296: E581-E591, 2009.
23. Zhou K, Chen Q, Chen J, Liang D, Feng W, Liu M, Wang Q, Wang R, Ouyang Q, Quan C and Chen S: Spatiotemporal regulation of insulin signaling by liquid-liquid phase separation. Cell Discov 8: 64, 2022.
24. Cantley LC: The phosphoinositide 3-kinase pathway. Science 296: 1655-1657, 2002.
25. Van Gerwen J, Shun-Shion AS and Fazakerley DJ: Insulin signalling and GLUT4 trafficking in insulin resistance. Biochem Soc Trans 51: 1057-1069, 2023.
26. Cao Y, Sun W and Xu G: Fuzhu jiangtang granules combined with metformin reduces insulin resistance in skeletal muscle of diabetic rats via PI3K/Akt signaling. Pharm Biol 57: 660-668, 2019.
27. Chen H, Li J, Zhang Y, Zhang W, Li X, Tang H, Liu Y, Li T, He H, Du B, *et al*: Bisphenol F suppresses insulin-stimulated glucose metabolism in adipocytes by inhibiting IRS-1/PI3K/AKT pathway. Ecotoxicol Environ Saf 231: 113201, 2022.
28. Zhu S, Sun F, Li W, Cao Y, Wang C, Wang Y, Liang D, Zhang R, Zhang S, Wang H and Cao F: Apelin stimulates glucose uptake through the PI3K/Akt pathway and improves insulin resistance in 3T3-L1 adipocytes. Mol Cell Biochem 353: 305-313, 2011.
29. Malone JI and Hansen BC: Does obesity cause type 2 diabetes mellitus (T2DM)? Or is it the opposite? Pediatr Diabetes 20: 5-9, 2019.
30. Watt MJ, Miotto PM, De Nardo W and Montgomery MK: The liver as an endocrine organ-linking NAFLD and insulin resistance. Endocr Rev 40: 1367-1393, 2019.
31. Petersen MC and Shulman GI: Mechanisms of insulin action and insulin resistance. Physiol Rev 98: 2133-2223, 2018.
32. Eckstein SS, Weigert C and Lehmann R: Divergent roles of IRS (Insulin Receptor Substrate) 1 and 2 in liver and skeletal muscle. Curr Med Chem 24: 1827-1852, 2017.
33. Fan Y, He Z, Wang W, Li J, Hu A, Li L, Yan L, Li Z and Yin Q: Tangganjian decoction ameliorates type 2 diabetes mellitus and nonalcoholic fatty liver disease in rats by activating the IRS/PI3K/AKT signaling pathway. Biomed Pharmacother 106: 733-737, 2018.
34. Lee J and Kim MS: The role of GSK3 in glucose homeostasis and the development of insulin resistance. Diabetes Res Clin Pract 77 (Suppl 1): S49-S57, 2007.
35. Guo X, Sun W, Luo G, Wu L, Xu G, Hou D, Hou Y, Guo X, Mu X, Qin L and Liu T: Panax notoginseng saponins alleviate skeletal muscle insulin resistance by regulating the IRS1-PI3K-AKT signaling pathway and GLUT4 expression. FEBS Open Bio 9: 1008-1019, 2019.
36. Wang J, He Y, Yu D, Jin L, Gong X and Zhang B: Perilla oil regulates intestinal microbiota and alleviates insulin resistance through the PI3K/AKT signaling pathway in type-2 diabetic KKAy mice. Food Chem Toxicol 135: 110965, 2020.
37. Wang LY, Wang Y, Xu DS, Ruan KF, Feng Y and Wang S: MDG-1, a polysaccharide from Ophiopogon japonicus exerts hypoglycemic effects through the PI3K/Akt pathway in a diabetic KKAy mouse model. J Ethnopharmacol 143: 347-354, 2012.
38. Liu N, Cui X, Guo T, Wei X, Sun Y, Liu J, Zhang Y, Ma W, Yan W and Chen L: Baicalein ameliorates insulin resistance of HFD/STZ mice through activating PI3K/AKT signal pathway of liver and skeletal muscle in a GLP-1R-dependent manner. Antioxidants (Basel) 13: 1246, 2024.
39. Cui X, Qian DW, Jiang S, Shang EX, Zhu ZH and Duan JA: Scutellariae radix and coptidis rhizoma improve glucose and lipid metabolism in T2DM rats via regulation of the metabolic profiling and MAPK/PI3K/Akt signaling pathway. Int J Mol Sci 19: 3634, 2018.
40. Zhang S, Zhang S, Zhang Y, Wang H, Chen Y and Lu H: Activation of NRF2 by epiberberine improves oxidative stress and insulin resistance in T2DM mice and IR-HepG2 cells in an AMPK dependent manner. J Ethnopharmacol 327: 117931, 2024.
41. Liu M, Liu C, Zhaxi P, Kou X, Liu Y and Xue Z: Research progress on hypoglycemic effects and molecular mechanisms of flavonoids: A review. Antioxidants (Basel) 14: 378, 2025.
42. Yang Z, Huang W, Zhang J, Xie M and Wang X: Baicalein improves glucose metabolism in insulin resistant HepG2 cells. Eur J Pharmacol 854: 187-193, 2019.
43. Li QP, Dou YX, Huang ZW, Chen HB, Li YC, Chen JN, Liu YH, Huang XQ, Zeng HF, Yang XB, *et al*: Therapeutic effect of oxyberberine on obese non-alcoholic fatty liver disease rats. Phytomedicine 85: 153550, 2021.
44. Entezari M, Hashemi D, Taheriazam A, Zabolian A, Mohammadi S, Fakhri F, Hashemi M, Hushmandi K, Ashrafizadeh M, Zarrabi A, *et al*: AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation. Biomed Pharmacother 146: 112563, 2022.

45. Lee YW and Pyo YH: Monascus-fermented grain vinegar enhances glucose homeostasis through the IRS-1/PI3K/Akt and AMPK signaling pathways in HepG2 cell and db/db mice. Food Sci Biotechnol 31: 1583-1591, 2022.
46. Xia X, Xu J, Wang X, Wang H, Lin Z, Shao K, Fang L, Zhang C and Zhao Y: Jiaogulan tea (Gpostemma pentaphyllum) potentiates the antidiabetic effect of white tea via the AMPK and PI3K pathways in C57BL/6 mice. Food Funct 11: 4339-4355, 2020.
47. Wang P, Liu Y, Kang SY, Lyu C, Han X, Ho T, Lee KJ, Meng X, Park YK and Jung HW: Clean-DM1, a Korean polyherbal formula, improves high fat diet-induced diabetic symptoms in mice by regulating IRS/PI3K/AKT and AMPK expressions in pancreas and liver tissues. Chin J Integr Med 30: 125-134, 2024.
48. Sharma BR, Kim HJ and Rhyu DY: Caulerpa lentillifera extract ameliorates insulin resistance and regulates glucose metabolism in C57BL/KsJ-db/db mice via PI3K/AKT signaling pathway in myocytes. J Transl Med 13: 62, 2015.
49. Arden C, Hampson LJ, Huang GC, Shaw JA, Aldibbiat A, Holliman G, Manas D, Khan S, Lange AJ and Agius L: A role for PFK-2/FBPase-2, as distinct from fructose 2,6-bisphosphate, in regulation of insulin secretion in pancreatic beta-cells. Biochem J 411: 41-51, 2008.
50. Nie Q, Chen H, Hu J, Fan S and Nie S: Dietary compounds and traditional Chinese medicine ameliorate type 2 diabetes by modulating gut microbiota. Crit Rev Food Sci Nutr 59: 848-863, 2019.
51. Gong X, Xiong L, Bi C and Zhang B: Diosmetin ameliorate type 2 diabetic mellitus by up-regulating Corynebacterium glutamicum to regulate IRS/PI3K/AKT-mediated glucose metabolism disorder in KK-Ay mice. Phytomedicine 87: 153582, 2021.
52. Gong P, Xiao X, Wang S, Shi F, Liu N, Chen X, Yang W, Wang L and Chen F: Hypoglycemic effect of astragaloside IV via modulating gut microbiota and regulating AMPK/SIRT1 and PI3K/AKT pathway. J Ethnopharmacol 281: 114558, 2021.
53. Tan Y, Miao L, Xiao J and Cheang WS: 3,3',4,5'-Tetramethoxy-trans-stilbene improves insulin resistance by activating the IRS/PI3K/Akt pathway and inhibiting oxidative stress. Curr Issues Mol Biol 44: 2175-2185, 2022.
54. Feng M, Liu F, Xing J, Zhong Y and Zhou X: Anemarrhena saponins attenuate insulin resistance in rats with high-fat diet-induced obesity via the IRS-1/PI3K/AKT pathway. J Ethnopharmacol 277: 114251, 2021.
55. Yang Q, Wen YM, Shen J, Chen MM, Wen JH, Li ZM, Liang YZ and Xia N: Guava leaf extract attenuates insulin resistance via the PI3K/Akt signaling pathway in a type 2 diabetic mouse model. Diabetes Metab Syndr Obes 13: 713-718, 2020.
56. Xiao H, Sun X, Lin Z, Yang Y, Zhang M, Xu Z, Liu P, Liu Z and Huang H: Gentiopicroside targets PAQR3 to activate the PI3K/AKT signaling pathway and ameliorate disordered glucose and lipid metabolism. Acta Pharm Sin B 12: 2887-2904, 2022.
57. Xu S, Chen Y and Gong Y: Improvement of theaflavins on glucose and lipid metabolism in diabetes mellitus. Foods 13: 1763, 2024.
58. Yaribeygi H, Sathyapalan T, Atkin SL and Sahebkar A: Molecular Mechanisms Linking Oxidative Stress and Diabetes Mellitus. Oxid Med Cell Longev 2020: 8609213, 2020.
59. Wang GY, Yan PY, Liu W, Liu LK, Li JP and Zeng Y: Potentilla bifurca flavonoids effectively improve insulin resistance. Eur Rev Med Pharmacol Sci 26: 8358-8369, 2022.
60. Jiang Z, Zhao M, Voilquin L, Jung Y, Aikio MA, Sahai T, Dou FY, Roche AM, Carcamo-Orive I, Knowles JW, *et al*: Isthmin-1 is an adipokine that promotes glucose uptake and improves glucose tolerance and hepatic steatosis. Cell Metab 33: 1836-1852.e11, 2021.
61. Kong WH, Oh SH, Ahn YR, Kim KW, Kim JH and Seo SW: Antiobesity effects and improvement of insulin sensitivity by 1-deoxynojirimycin in animal models. J Agric Food Chem 56: 2613-2619, 2008.
62. Liu Q, Li X, Li C, Zheng Y and Peng G: 1-Deoxynojirimycin alleviates insulin resistance via activation of insulin signaling PI3K/AKT pathway in skeletal muscle of db/db mice. Molecules 20: 21700-21714, 2015.
63. Kang CW, Park M and Lee HJ: Mulberry (Morus alba L.) leaf extract and 1-deoxynojirimycin improve skeletal muscle insulin resistance via the activation of IRS-1/PI3K/Akt pathway in db/db mice. Life (Basel) 12: 1630, 2022.
64. LaMoia TE and Shulman GI: Cellular and molecular mechanisms of metformin action. Endocr Rev 42: 77-96, 2021.
65. Garabadu D and Krishnamurthy S: Metformin attenuates hepatic insulin resistance in type-2 diabetic rats through PI3K/Akt/GLUT-4 signalling independent to bicuculline-sensitive GABAA receptor stimulation. Pharm Biol 55: 722-728, 2017.
66. Sundaresan A, Radhiga T and Pugalendi KV: Ursolic acid and rosiglitazone combination improves insulin sensitivity by increasing the skeletal muscle insulin-stimulated IRS-1 tyrosine phosphorylation in high-fat diet-fed C57BL/6J mice. J Physiol Biochem 72: 345-352, 2016.
67. Li Z, Zhu Y, Li C, Tang Y, Jiang Z, Yang M, Ni CL, Li D, Chen L and Niu W: Liraglutide ameliorates palmitate-induced insulin resistance through inhibiting the IRS-1 serine phosphorylation in mouse skeletal muscle cells. J Endocrinol Invest 41: 1097-1102, 2018.
68. He J, Fan F, Li J, Han Y, Song Y, Zhang R, Xu Y, Wu H and Fan R: SIRT1 alleviates insulin resistance and respiratory distress in late preterm rats by activating QKI5-mediated PPARγ/PI3K/AKT pathway. Cell Cycle 22: 2449-2466, 2023.
69. Dai HB, Wang HY, Wang FZ, Qian P, Gao Q, Zhou H and Zhou YB: Adrenomedullin ameliorates palmitic acid-induced insulin resistance through PI3K/Akt pathway in adipocytes. Acta Diabetol 59: 661-673, 2022.
70. Luo X, Li RR, Li YQ, Yu HP, Yu HN, Jiang WG and Li YN: Reducing VEGFB expression regulates the balance of glucose and lipid metabolism in mice via VEGFR1. Mol Med Rep 26: 285, 2022.
71. Li Y, Li W, Zhu X, Xu N, Meng Q, Jiang W, Zhang L, Yang M, Xu F and Li Y: VEGFB ameliorates insulin resistance in NAFLD via the PI3K/AKT signal pathway. J Transl Med 22: 976, 2024.
72. Guan X, Jiang L, Cai L, Zhang L and Hu X: A new co-crystal of synthetic drug rosiglitazone with natural medicine berberine: Preparation, crystal structures, and dissolution. Molecules 25: 4288, 2020.
73. He Q, Chen B, Wang G, Zhou D, Zeng H, Li X, Song Y, Yu X, Liang W, Chen H, *et al*: Co-crystal of rosiglitazone with berberine ameliorates hyperglycemia and insulin resistance through the PI3K/AKT/TXNIP pathway in vivo and in vitro. Front Pharmacol 13: 842879, 2022.
74. Li Y, Tang Y, Shi S, Gao S, Wang Y, Xiao D, Chen T, He Q, Zhang J and Lin Y: Tetrahedral framework nucleic acids ameliorate insulin resistance in type 2 diabetes mellitus via the PI3K/Akt pathway. ACS Appl Mater Interfaces 13: 40354-40364, 2021.
75. Li YZ, Di Cristofano A and Woo M: Metabolic role of PTEN in insulin signaling and resistance. Cold Spring Harb Perspect Med 10: a036137, 2020.
76. Chen G, Fan XY, Zheng XP, Jin YL, Liu Y and Liu SC: Human umbilical cord-derived mesenchymal stem cells ameliorate insulin resistance via PTEN-mediated crosstalk between the PI3K/Akt and Erk/MAPKs signaling pathways in the skeletal muscles of db/db mice. Stem Cell Res Ther 11: 401, 2020.
77. Aierken A, Li B, Liu P, Cheng X, Kou Z, Tan N, Zhang M, Yu S, Shen Q, Du X, *et al*: Melatonin treatment improves human umbilical cord mesenchymal stem cell therapy in a mouse model of type II diabetes mellitus via the PI3K/AKT signaling pathway. Stem Cell Res Ther 13: 164, 2022.
78. Chen T, Zhang Y, Liu Y, Zhu D, Yu J, Li G, Sun Z, Wang W, Jiang H and Hong Z: MiR-27a promotes insulin resistance and mediates glucose metabolism by targeting PPAR-γ-mediated PI3K/AKT signaling. Aging (Albany NY) 11: 7510-7524, 2019.
79. Zhong FY, Li J, Wang YM, Chen Y, Song J, Yang Z, Zhang L, Tian T, Hu YF and Qin ZY: MicroRNA-506 modulates insulin resistance in human adipocytes by targeting S6K1 and altering the IRS1/PI3K/AKT insulin signaling pathway. J Bioenerg Biomembr 53: 679-692, 2021.
80. Lv Z, Ren Y, Li Y, Niu F, Li Z, Li M, Li X, Li Q, Huang D, Yu Y, *et al*: RNA-binding protein GIGYF2 orchestrates hepatic insulin resistance through STAU1/PTEN-mediated disruption of the PI3K/AKT signaling cascade. Mol Med 30: 124, 2024.
81. Sun J, Wu K, Wang P, Wang Y, Wang D, Zhao W, Zhao Y, Zhang C and Zhao X: Dietary tomato pectin attenuates hepatic insulin resistance and inflammation in high-fat-diet mice by regulating the PI3K/AKT pathway. Foods 13: 444, 2024.
82. Jeong O and Kim HS: Dietary chokeberry and dried jujube fruit attenuates high-fat and high-fructose diet-induced dyslipidemia and insulin resistance via activation of the IRS-1/PI3K/Akt pathway in C57BL/6 J mice. Nutr Metab (Lond) 16: 38, 2019.
83. Liu J, Wang X, Zhu Y, Deng H, Huang X, Jayavanth P, Xiao Y, Wu J and Jiao R: Theabrownin from dark tea ameliorates insulin resistance via attenuating oxidative stress and modulating IRS-1/PI3K/Akt pathway in HepG2 cells. Nutrients 15: 3862, 2023.

84. Yu W, Fan L, Wang M, Cao B and Hu X: pterostilbene improves insulin resistance caused by advanced glycation end products (AGEs) in hepatocytes and mice. Mol Nutr Food Res 65: e2100321, 2021.
85. Mutt SJ, Raza GS, Mäkinen MJ, Keinänen-Kiukaanniemi S, Järvelin MR and Herzig KH: Vitamin D deficiency induces insulin resistance and re-supplementation attenuates hepatic glucose output via the PI3K-AKT-FOXO1 mediated pathway. Mol Nutr Food Res 64: e1900728, 2020.
86. Huang X, Liu G, Guo J and Su Z: The PI3K/AKT pathway in obesity and type 2 diabetes. Int J Biol Sci 14: 1483-1496, 2018.
87. Tremblay F, Brûlé S, Hee Um S, Li Y, Masuda K, Roden M, Sun XJ, Krebs M, Polakiewicz RD, Thomas G and Marette A: Identification of IRS-1 Ser-1101 as a target of S6K1 in nutrient- and obesity-induced insulin resistance. Proc Natl Acad Sci USA 104: 14056-14061, 2007.
88. Wu YS, Li ZM, Chen YT, Dai SJ, Zhou XJ, Yang YX, Lou JS, Ji LT, Bao YT, Xuan L, *et al*: Berberine improves inflammatory responses of diabetes mellitus in zucker diabetic fatty rats and insulin-resistant HepG2 cells through the PPM1B pathway. J Immunol Res 2020: 2141508, 2020.
89. Flores-Opazo M, McGee SL and Hargreaves M: Exercise and GLUT4. Exerc Sport Sci Rev 48: 110-118, 2020.
90. Jayaraman S, Krishnamoorthy K, Prasad M, Veeraraghavan VP, Krishnamoorthy R, Alshuniaber MA, Gatasheh MK, Elrobh M and Gunassekaran: Glyphosate potentiates insulin resistance in skeletal muscle through the modulation of IRS-1/PI3K/Akt mediated mechanisms: An in vivo and in silico analysis. Int J Biol Macromol 242 (Pt 2): 124917, 2023.
91. Zhong RF, Liu CJ, Hao KX, Fan XD and Jiang JG: Polysaccharides from Flos Sophorae Immaturus ameliorates insulin resistance in IR-HepG2 cells by co-regulating signaling pathways of AMPK and IRS-1/PI3K/AKT. Int J Biol Macromol 280 (Pt 4): 136088, 2024.
92. Wang DS, Wang JM, Zhang FR, Lei FJ, Wen X, Song J, Sun GZ and Liu Z: Ameliorative effects of malonyl ginsenoside from panax ginseng on glucose-lipid metabolism and insulin resistance via IRS1/PI3K/Akt and AMPK signaling pathways in type 2 diabetic mice. Am J Chin Med 50: 863-882, 2022.
93. Hassan MA, Elmageed GMA, El-Qazaz IG, El-Sayed DS, El-Samad LM and Abdou HM: The synergistic influence of polyflavonoids from citrus aurantifolia on diabetes treatment and their modulation of the PI3K/AKT/FOXO1 signaling pathways: Molecular docking analyses and in vivo investigations. Pharmaceutics 15: 2306, 2023.
94. Yan J, Wang C, Jin Y, Meng Q, Liu Q, Liu Z, Liu K and Sun H: Catalpol ameliorates hepatic insulin resistance in type 2 diabetes through acting on AMPK/NOX4/PI3K/AKT pathway. Pharmacol Res 130: 466-480, 2018.
95. Xu Z, Cai K, Su SL, Zhu Y, Liu F and Duan JA: Salvianolic acid B and tanshinone IIA synergistically improve early diabetic nephropathy through regulating PI3K/Akt/NF-κB signaling pathway. J Ethnopharmacol 319 (Pt 3): 117356, 2024.
96. Alaaeldin R, Abdel-Rahman IAM, Hassan HA, Youssef N, Allam AE, Abdelwahab SF, Zhao QL and Fathy M: Carpachromene ameliorates insulin resistance in HepG2 cells via modulating IR/IRS1/PI3k/Akt/GSK3/FoxO1 pathway. Molecules 26: 7629, 2021.
97. Savova MS, Mihaylova LV, Tews D, Wabitsch M and Georgiev MI: Targeting PI3K/AKT signaling pathway in obesity. Biomed Pharmacother 159: 114244, 2023.
98. Zhou YJ, Xu N, Zhang XC, Zhu YY, Liu SW and Chang YN: Chrysin improves glucose and lipid metabolism disorders by regulating the AMPK/PI3K/AKT signaling pathway in insulin-resistant HepG2 Cells and HFD/STZ-Induced C57BL/6J Mice. J Agric Food Chem 69: 5618-5627, 2021.
99. Feng SY, Wu SJ, Chang YC, Ng LT and Chang SJ: Stimulation of GLUT4 Glucose uptake by anthocyanin-rich extract from black rice (Oryza sativa L.) via PI3K/Akt and AMPK/p38 MAPK signaling in C2C12 cells. Metabolites 12: 856, 2022.
100. Zhao H, Zhai BW, Zhang MY, Huang H, Zhu HL, Yang H, Ni HY and Fu YJ: Phlorizin from Lithocarpus litseifolius [Hance] Chun ameliorates FFA-induced insulin resistance by regulating AMPK/PI3K/AKT signaling pathway. Phytomedicine 130: 155743, 2024.
101. Zhang H, Ma L, Peng W, Wang B and Sun Y: Association between gut microbiota and onset of type 2 diabetes mellitus: A two-sample Mendelian randomization study. Front Cell Infect Microbiol 14: 1327032, 2024.
102. Takeuchi T, Kubota T, Nakanishi Y, Tsugawa H, Suda W, Kwon ATJ, Yazaki J, Ikeda K, Nemoto S, Mochizuki Y, *et al*: Gut microbial carbohydrate metabolism contributes to insulin resistance. Nature 621: 389-395, 2023.
103. Zhao SL, Liu D, Ding LQ, Liu GK, Yao T, Wu LL, Li G, Cao SJ, Qiu F and Kang N: Schisandra chinensis lignans improve insulin resistance by targeting TLR4 and activating IRS-1/PI3K/AKT and NF-κB signaling pathways. Int Immunopharmacol 142 (Pt A): 113069, 2024.
104. Zhang Y, Yang S, Zhang M, Wang Z, He X, Hou Y and Bai G: Glycyrrhetinic acid improves insulin-response pathway by regulating the balance between the Ras/MAPK and PI3K/Akt pathways. Nutrients 11: 604, 2019.
105. Zhou J, Shi Y, Yang C, Lu S, Zhao L, Liu X, Zhou D, Luo L and Yin Z: γ-glutamylcysteine alleviates insulin resistance and hepatic steatosis by regulating adenylate cyclase and IGF-1R/IRS1/PI3K/Akt signaling pathways. J Nutr Biochem 119: 109404, 2023.
106. Guo X, Yin T, Chen D, Xu S, Ye R and Zhang Y: Astragaloside IV regulates insulin resistance and inflammatory response of adipocytes via modulating MIR-21/PTEN/PI3K/AKT signaling. Endocr Metab Immune Disord Drug Targets 23: 1538-1547, 2023.
107. Deng A, Wang Y, Huang K, Xie P, Mo P, Liu F, Chen J, Chen K, Wang Y and Xiao B: Artichoke (Cynara scolymus L.) water extract alleviates palmitate-induced insulin resistance in HepG2 hepatocytes via the activation of IRS1/PI3K/AKT/FoxO1 and GSK-3β signaling pathway. BMC Complement Med Ther 23: 460, 2023.
108. Rathinaswamy MK and Burke JE: Class I phosphoinositide 3-kinase (PI3K) regulatory subunits and their roles in signaling and disease. Adv Biol Regul 75: 100657, 2019.
109. Kim Y, Rouse M, González-Mariscal I, Egan JM and O'Connell JF: Dietary curcumin enhances insulin clearance in diet-induced obese mice via regulation of hepatic PI3K-AKT axis and IDE, and preservation of islet integrity. Nutr Metab (Lond) 16: 48, 2019.
110. Chen Z, Liu H, Lei S, Zhao B and Xia Z: LY294002 prevents lipopolysaccharide-induced hepatitis in a murine model by suppressing IκB phosphorylation. Mol Med Rep 13: 811-816, 2016.
111. Shiwa M, Yoneda M, Okubo H, Ohno H, Kobuke K, Monzen Y, Kishimoto R, Nakatsu Y, Asano T and Kohno N: Distinct time course of the decrease in hepatic AMP-Activated protein kinase and Akt phosphorylation in mice fed a high fat diet. PLoS One 10: e0135554, 2015.
112. Lalli CA, Pauli JR, Prada PO, Cintra DE, Ropelle ER, Velloso LA and Saad MJ: Statin modulates insulin signaling and insulin resistance in liver and muscle of rats fed a high-fat diet. Metabolism 57: 57-65, 2008.
113. Wang CC, Adochio RL, Leitner JW, Abeyta IM, Draznin B and Cornier MA: Acute effects of different diet compositions on skeletal muscle insulin signalling in obese individuals during caloric restriction. Metabolism 62: 595-603, 2013.
114. Cho H, Lai CC, Bonnavion R, Alnouri MW, Wang S, Roquid KA, Kawase H, Campos D, Chen M, Weinstein LS, *et al*: Endothelial insulin resistance induced by adrenomedullin mediates obesity-associated diabetes. Science 387: 674-682, 2025.