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Review Article

Iridoid terpenoids: a class of promising compounds to regulate blood glucose

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Abstract: Iridoids derived from plants have demonstrated promising effects in regulating glycemic levels, which have captured the attention of researchers. Thus, an overview of iridoids with hypoglycemic activity, with a particular focus on their potential mechanisms of action in various cellular and animal models was summarized. It has been observed that iridoids primarily exert anti-inflammatory, antioxidant, and hypoglycemic effects through signaling pathways such as NF-κB, MAPK, AMPK, PI3K/AKT, NLRP3, ROS, NOX4, and AGEs/RAGE, thereby mitigating the symptoms of diabetes and its complications. By comprehensively summarizing and analyzing the molecular pathways through which iridoids alleviate diabetes and its complications, this review aims to establish a scientific foundation for the utilization of iridoids.

Keywords: iridoids; diabetes; mechanisms; signaling pathways

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1 Introduction

Iridoids are commonly found in plants as naturally occurring secondary metabolites, particularly in *Genisteinae*, *Rubiaceae*, *Labiatae*, and *Gentianaceae*, which are relatively abundant. Due to their unstable nature, iridoids are primarily present in the form of glycosides[1]. According to incomplete statistics, over 800 iridoids have been isolated and identified in plants[2]. These compounds exhibit a variety of important pharmacological activities, such as anti-inflammatory, antioxidant, hypoglycemic, and antitumor effects[3-6]. Among them, more than 10 iridoids such as geniposide[7], catalpol[8], loganin[9], and oleuropein[10] have demonstrated significant hypoglycemic effects at the cellular and animal levels. They can effectively alleviate diabetes and its complications.

Diabetes is a complex chronic metabolic disease characterized by insufficient insulin secretion or peripheral insulin resistance, leading to abnormally elevated blood glucose levels[11]. Previous studies have shown that the treatment mechanism for diabetes focuses on signaling pathways related to inflammation, oxidative stress, insulin signaling, and glucolipid metabolism. In addition, researchers have been continuously exploring diabetes treatments that target the gut flora[12]. However, the mechanism of action of iridoids in diabetes needs further elucidation. In this review, the molecular pathways through which iridoids alleviate diabetes and its complications are discussed (Fig. 1).

This article reviews the mechanisms and targets of iridoid compounds for the treatment of diabetes and its complications in recent years (Table 1), aiming to contribute to the further research, development, and utilization of iridoid compounds.

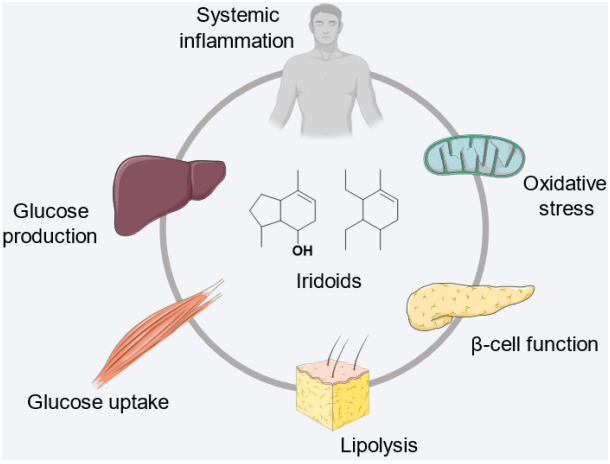

Figure 1 Effect of iridoids on diabetes.

2 Mechanisms of action of iridoids in alleviating diabetes mellitus and its complications

2.1 Through signaling pathways related to inflammation

Inflammation plays a crucial role in promoting the onset and

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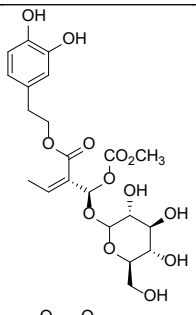
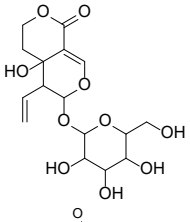
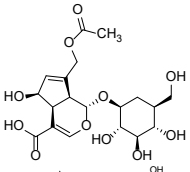
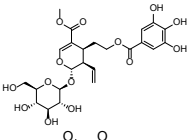
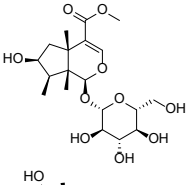
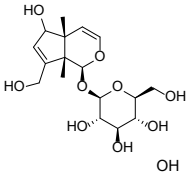
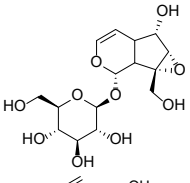
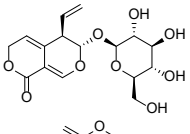
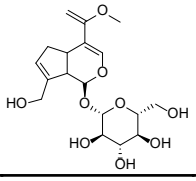
Table 1 Iridoid compounds that alleviate diabetes and its complications

Compounds	Molecular formula	Structure	Source of plants	Pharmacological activity
Oleuropein	$C_{25}H_{32}O_{13}$		*Olea europaea* L	Anti-inflammatory, anti-oxidation, anti-cancer, hypoglycemic
Swertiamarin	$C_{16}H_{22}O_{10}$		*Swertia patens*	Anti-inflammatory, liver protection, blood lipid regulation, anti-diabetes
Asperulosidic acid	$C_{18}H_{24}O_{12}$		*Hedyotis diffusa* Willd	Anti-tumor, antioxidant and anti-inflammatory
Cornuside	$C_{24}H_{30}O_{14}$		*Cornus officinalis* Sieb. et Zucc.	Anti-inflammatory, anti-apoptotic and modulating mitochondrial dysfunction
Loganin	$C_{17}H_{26}O_{10}$		*Cornus officinalis* Sieb. et Zucc.	Anti-inflammatory, anti-oxidation, anti-shock
Aucubin	$C_{15}H_{22}O_9$		*Eucommia ulmoides* Oliv.	Anti-inflammation, anti-oxidation, anti-aging, liver protection, anti-tumor
Catalpol	$C_{15}H_{22}O_{10}$		Rehmannia glutinosa	Hypoglycemic, anti-inflammatory, anti-cancer, anti-oxidation
Gentiopicroside	$C_{16}H_{20}O_9$		*Gentiana scabra* Bge.	Hepatoprotective, cholangial, analgesic, anti-inflammatory, antibacterial, stomach-strengthening and anti-tumor
Geniposide	$C_{17}H_{24}O_{10}$		*Gardenia jasminoides* Ellis	Anti-diabetic, anti-oxidative, anti-proliferative, neuroprotective

progression of diabetes. Numerous studies have demonstrated that inflammation can lead to insulin resistance and dysfunction of pancreatic β-cells. Targeting signaling pathways associated with inflammation may prove to be an effective strategy for preventing and managing diabetes mellitus and its related complications[13-15].

The nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways are key pathways that regulate immune responses, inflammation, and other physiological processes. Their abnormal activation is associated with various diseases and is an important target for drug

development[16,17]. Research has shown that the iridoids oleuropein[18], swertiamarin[19], and asperulosidic acid[20] can reduce the inflammatory response at the cellular or animal level by inhibiting the NF-κB and MAPK signaling pathways. This protection helps guard against diabetes-associated organ damage and promotes the alleviation of insulin resistance. Cornuside, Loganin, and Aucubin can inhibit NF-κB activation, reduce the levels of pro-inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), and alleviate symptoms in diabetic mice[9,21-23]. Catalpol significantly inhibits the c-Jun N-terminal kinase (JNK) and NF-κB signaling pathways in adipose tissue and improves insulin resistance and adipose tissue inflammation induced by a high-fat diet (HFD)[24]. Catalpol also activates the adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)/silent mating type information regulation 2 homolog-1 (SIRT1)/NF-κB pathway, effectively attenuating inflammation-induced kidney injury[25]. Furthermore, gentiopicroside can increase takeda G protein-coupled receptor 5 (TGR5) protein levels and promote the interaction between IκB α and β-arrestin2. It inhibits the phosphorylation and degradation of IκB α, blocking nuclear translocation of NF-κB p65 and preventing renal inflammation in diabetic mice[26].

The NOD-like receptor protein 3 (NLRP3) inflammasome is a cytoplasmic multiprotein complex. When activated, the NLRP3 inflammasome can regulate the body's inflammatory response and related cellular functions by mediating the maturation and release of various pro-inflammatory factors. Its abnormal activation has been linked to various inflammatory diseases, such as diabetes and cancer[27]. Loganin inhibited NLRP3 inflammatory vesicle activation, reduced inflammatory factor levels, attenuated cellular pyroptosis, and alleviated diabetic injury *in vitro* and *in vivo*[28,29]. Aucubin can alleviate NLRP3 inflammasome activation and the inflammatory response by inhibiting the endoplasmic reticulum (ER) stress-mediated inositol-requiring enzyme 1 alpha (IRE1α)/thioredoxin-interacting protein (TXNIP) signaling pathway via the recombinant NADPH oxidase 4(NOX4)/reactive oxygen species (ROS) pathway. Thus, it can ameliorate liver injury and fibrosis in type 2 diabetes mice[30]. Swertiamarin improves the imbalance of inflammatory factors and reduces peripheral neuralgia in diabetic rats by inhibiting the NOXs/ROS/NLRP3 signaling pathway[31].

In addition, gentiopicroside alleviates cardiac inflammation and fibrosis in rats with type 2 diabetes by targeting the MH2 structural domain of Smad3, a major effector molecule in transforming growth factor-beta (TGF-β) signaling, and blocking high glucose-induced phosphorylation[32]. Geniposide significantly enhances lesion retraction, reduces inflammatory cell infiltration and fibroblast proliferation in the central lesion area, decreases pro-inflammatory factors, and increases anti-inflammatory factors. This promotes wound healing in diabetic rats[33,34].

Therefore, at present, some iridoids alleviate diabetes and its complications mainly through inflammation-related signaling pathways such as NF-κB, MAPK, NLRP3 and TGF-β (Fig. 2).

2.2 Through signaling pathways related to oxidative stress

Both oxidative stress and inflammation are important potential factors contributing to the pathological development of metabolic diseases, including diabetes. Oxidative stress is a state of imbalance between the oxidative and antioxidant systems of cells and tissues, resulting in the overproduction of oxidized free radicals and ROS. The overproduction of ROS has been associated with insulin resistance, hyperglycemia, inflammation, and metabolic disorders[35-37]. Loganin inhibits the production of ROS and the activation of NLRP3 inflammatory vesicles to exert antioxidant effects. As a result, it attenuates cellular pyroptosis in Schwann cells induced by high glucose[29]. Additionally, both loganin and iridoids from *Cornus officinalis* inhibit the advanced glycation end-products (AGEs)/receptorfor advanced glycation end products (RAGE)/p38MAPK signaling pathway, significantly reduce ROS levels, and attenuate AGEs-induced diabetic testicular damage[38,39]. Asperulosidic acid can regulate the extracellular signal-regulated kinase 1/2 (ERK1/2) and p38MAPK signaling pathways by inhibiting oxidative stress-related biomarkers and alleviate placental oxidative stress in mice with gestational diabetes[20]. Catalpol can inhibit the AGEs/RAGE/Nox4 signaling pathway, significantly downregulate ROS levels, restore super

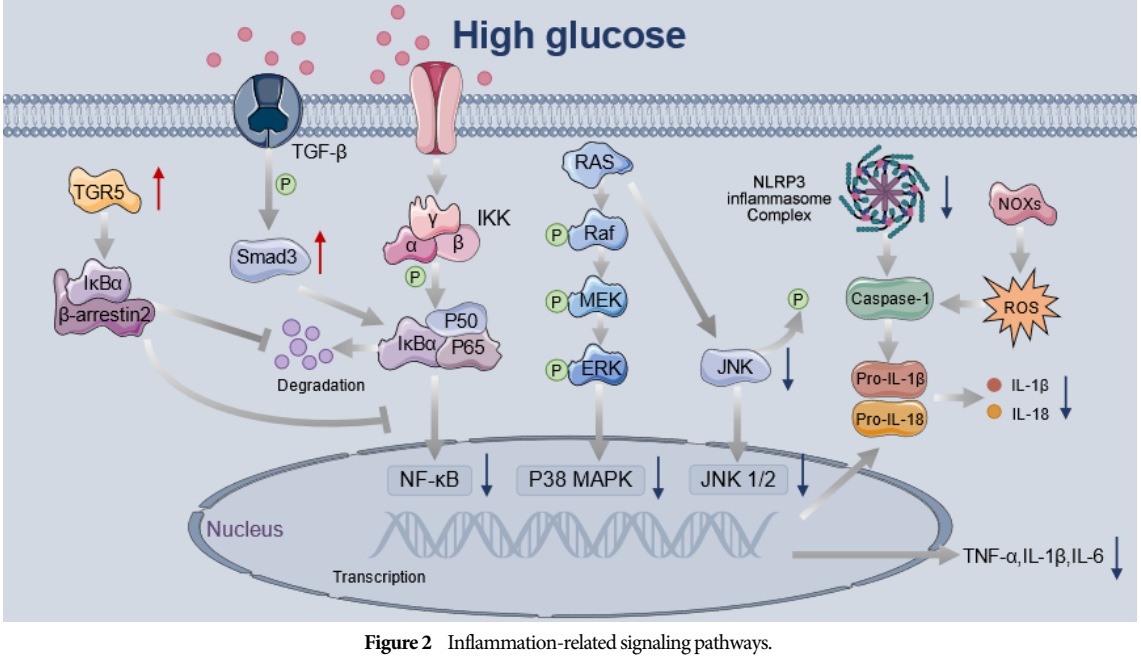


Figure 2 Inflammation-related signaling pathways.

oxide dismutase (SOD) activity, and exhibit considerable antioxidant effects both *in vivo* and *in vitro*[40].

Catalpol also activates hepatic AMPK and inhibits NOX4-mediated oxidative stress[41]. In addition, catalpol can prevent diabetes-induced hepatic oxidative stress by upregulating miR-96-5p levels and targeting the p66shc mRNA 3'UTR to inhibit the p66shc/cytochrome C cascade [42]. Geniposide can improve diabetic nephropathy by reducing oxidative stress through the activation of AMPK[43]. Swertiamarin can alleviate hepatic oxidative stress in fructose-fed mice by activating nuclear factor erythroid 2-related factor 2 (Nrf2) decreasing xanthine oxidase (XO), and enhancing the enzymes of the antioxidant defense system[44]. Aucubin promotes endogenous antioxidant defenses and alleviates diabetic nephropathy through the SIRT1/SIRT3-forkhead box O3A (FOXO3a) signaling pathway[23]. In general, the specific signals of iridoid compounds ameliorating diabetes through oxidative stress were mainly focused on ROS, NRF2, MAPK/NF-κB, AMPK and FOXO3a (Fig. 3).

2.3 Through signaling pathways related to insulin

Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling is necessary for normal metabolism. The impairment of this pathway results in insulin resistance, obesity, and type 2 diabetes, which then further worsens the impairment of the PI3K/AKT pathway, creating a vicious cycle[45]. Researchers have found that enhancing AMPK signaling or interacting with other molecular pathways, such as PI3K/AKT, NOX4, peroxisome proliferators-activated receptor gamma coactivator 1 alpha (PGC-1α), and NF-κB, improves insulin resistance, glucolipid metabolism, and diabetic complications[46]. The concentrated fraction of iridoids from *Wendlandia glabrata* can regulate hepatic glucose metabolism by activating the AMPK/phosphoenolpyruvate carboxykinase (PEPCK)/glucose-6-phosphatase (G6Pase) signaling pathway, demonstrating significant hypoglycemic potential[47] (Fig. 4). Catalpol can significantly improve insulin sensitivity in the skeletal muscle of type 2 diabetic mice by activating the AMPK/SIRT1/PGC-1α/peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling pathway[48]. Jing Liu *et al*[49] found that the antidiabetic effects of catalpol in db/db mice were mainly related to glucose metabolism and the insulin signaling pathway, as shown by liver transcriptomics. The liver and skeletal muscle are key organs for insulin metabolism, and catalpol can improve hepatic insulin resistance in type 2 diabetic mice by activating the AMPK/NOX4/PI3K/AKT pathway[41]. Catalpol can also activate the insulin receptor substrate 1 (IRS-1)/PI3K/Akt/glucose transporter 4 (GLUT4) signaling pathway, which improves insulin resistance in skeletal muscle and lowers fasting glucose levels[48,50]. Iridoids extracted from *Corni fructus* (*C. fructus*) ctivate the PI3K/Akt pathway, significantly elevate the expression level of related proteins in skeletal muscle, and alleviate hyperglycemia[22,51]. Loganin can attenuate insulin resistance by modulating the JNK/IRS-1/Akt/glycogen synthase kinase-3 beta (GSK3β) signaling pathway in diabetic rats[9]. In addition, it has been found that overexpression of retinol-binding protein 4 (RBP4) causes insulin resistance. Geniposide not only reduces RBP4 levels but also disrupts the circulating RBP4 homeostasis regulated by transthyretin (TTR), thereby increasing insulin sensitivity in the liver and skeletal muscle of diabetic mice[5].

Researchers have also demonstrated the important role of the AMPK and PI3K/AKT signaling pathways in improving insulin resistance and promoting glucose uptake *in vitro*. Swertiamarin has been shown to increase the expression of insulin signaling proteins, including AMPK, IR, PI3K, and pAkt, while decreasing the expression of PEPCK. This reduction in PEPCK levels leads to a decrease in hepatic glucose production and fatty acid synthesis, ultimately improving insulin sensitivity in HepG2 cells[52]. Zhenhua Liu *et al.* isolated and characterized nine iridoids (compounds 1-9) from *Patrinia scabiosaefolia*. Compound 1 was found to promote glucose uptake in dexamethasone-treated 3T3-L1 adipocytes through the activation of the PI3K/Akt signaling pathway[53]. Kutkin demonstrated antidiabetic effects by enhancing insulin sensitivity and promoting glucose uptake through the activation of PI3K/Akt signaling in 3T3-L1 adipocytes[54]. *P. scabiosaefolia* iridoids activate the IRS-1/PI3K/Akt/GLUT4 signaling pathway to improve insulin resistance in 3T3-L1 adipocytes[55]. In addition, Oleuropein increased levels of Akt and

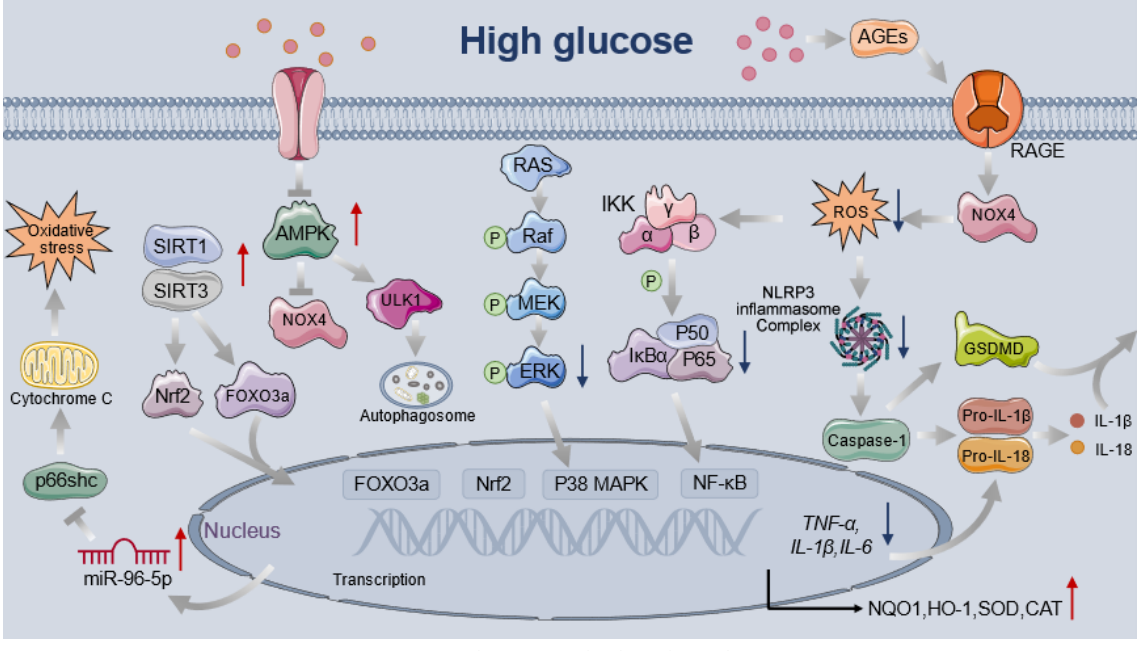


Figure 3 Oxidative stress-related signaling pathways.

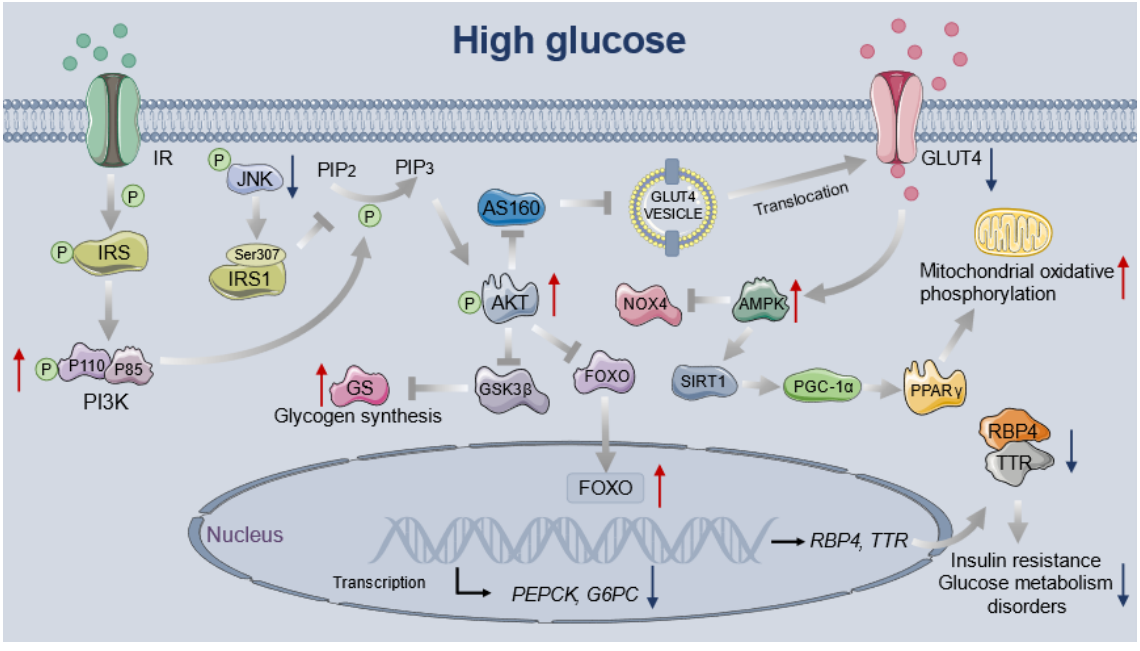


Figure 4 Insulin-related signaling pathways.

GLUT2, which had been inhibited by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), in INS-1 cells. This prevented damage to pancreatic β-cells caused by TCDD[56]. Finally, geniposide promotes autophagy in IR-HepG2 cells through the P62/NF-κB/GLUT-4 pathway, significantly improving insulin resistance in HepG2 cells[57].

2.4 Through signaling pathways related to apoptosis and pyroptosis

Various forms of programmed cell death, including apoptosis and pyroptosis, are considered to be important pathological mechanisms of diabetes and its complications. Inhibiting any form of cell death is an effective strategy for treating diabetes[58, 59]. Loganin can prevent high glucose-induced cellular pyroptosis by inhibiting ROS production and the NLRP3/Caspase-1/Gasdermin D (GSDMD) pathway in order to prevent high glucose-induced cellular pyroptosis[28, 29]. Both loganin and iridoids from *C. officinalis* significantly inhibited the AGEs/RAGE/p38MAPK signaling pathway, decreased the BCL2-associated X protein (Bax)/ B-cell lymphoma-2 (Bcl-2) ratio and alleviated AGE-induced diabetic testicular damage and germ cell apoptosis [38, 39]. Oleuropein regulates the MAPK signaling pathway and its downstream targets Bax, cysteine aspartate-specific protease 3 (caspase-3), and Bcl-2 expression to inhibit apoptosis and attenuate kidney injury in db/db (diabetic) mice[60].

2.5 Through enteral glucagon (GLP-1)

Glucagon-like peptide-1 (GLP-1) is a hormone similar to glucagon, produced in enteroendocrine cells and the brain. It inhibits delayed gastric emptying, reduces food intake, and regulates insulin and glucagon secretion, among other beneficial effects. These factors make GLP-1 a novel drug target for the development of therapeutic treatments for metabolic disorders such as obesity and diabetes mellitus[61-63]. Intake of oleuropein-rich chocolate was found to attenuate hyperglycemia in diabetic patients through a GLP-1-mediated mechanism[64]. The loganic acid in *Gentiana scabra* helps promote GLP-1 secretion, thereby lowering blood glucose[65]. Boschnaloside increases GLP-1 secretion and interacts with the extracellular structural domain of the GLP-1 receptor to enhance the proinsulinogenic effects of GLP-1, thereby ameliorating blood glucose abnormality and pancreatic islet dysfunction in diabetic mice[66].

2.6 Through the intestinal flora

Gut microbiota plays an important role in body metabolism and immune regulation. Its composition and dysfunction can trigger intestinal dysfunction, inflammation, and glucose metabolism dysfunction. More and more studies have found that patients with type 2 diabetes often have accompanying disorders of the intestinal flora. Therefore, the intestinal flora may be a new therapeutic target for improving diabetes mellitus and its complications[67-69]. Oleuropein administration was found to improve the composition and function of the intestinal microbiota, significantly reduce fasting glucose, and improve glucose tolerance as well as improve related histopathological features in db/db mice[70]. Asperuloside effectively inhibited the gut dysregulation induced by a HFD as well as altered intestinal-sourced secondary metabolites and metabolic signaling in HFD mice. It effectively inhibited weight gain, glucose intolerance, and insulin resistance in HFD mice[71]. Four extracts of *C. fructus*, including iridoids, enhance the production of short-chain fatty acids and modulate the composition of the gut microbiota. This leads to improved intestinal homeostasis in mice with type 2 diabetes[72]. Catalpol modulates the intestinal microbiota and increases levels of glycolytic metabolites, thereby ameliorating diabetes-induced testicular damage[73].

2.7 Others

Sweroside, arbortristoside-C, and iridoids from *C. Fructus* have demonstrated inhibitory effects on α-glucosidase and have potential therapeutic value for the treatment of diabetes[74-77]. Iridoids extracted from *C. Fructus* improve hepatic lipid metabolism in type 2 diabetes mice by modulating the AMPK/Acetyl-CoA carboxylase (ACC)/Carnitine palmitoyltransferase 1 (CPT-1) pathway[78]. Catalpol can slow down the progression of diabetic nephropathy by inhibiting the

RAGE/Ras homolog gene family, member A (RhoA)/Rho-associated protein kinase (ROCK) pathway. It also blocks angiogenesis of mGECs by inhibiting galectin-3. Furthermore, it activates the insulin-like growth factor 1 (IGF-1)/insulin-like growth factor 1 receptor (IGF-1R) signaling pathway by inhibiting recombinant growth factor receptor bound protein 10 (Grb10). Additionally, catalpol downregulates the mRNA expression of transforming growth factor- beta 1 (TGF-β1) and connective tissue growth factor (CTGF) in the renal cortex[79-82]. In addition, catalpol can improve podocyte injury by inhibiting RhoA, recombinant cell division cycle protein 42 (Cdc42), and mammalian target of rapamycin (mTOR) activities, and promoting transcription factor EB (TFEB) nuclear translocation[83]. It can also attenuate myocardial injury in diabetic cardiomyopathic mice through the nuclear paraspeckle assembly transcript 1 (Neat1)/miR-140-5p/recombinant histone deacetylase 4 (HDAC4) pathway[84], and improve neointimal hyperplasia in hyperglycemic rat neointimal hyperplasia through the downregulation of monocyte chemotactic protein-1 (MCP-1) expression in the carotid artery[85]. Catalpol exerts a hypoglycemic effect by enhancing myogenic differentiation (MyoD)/MyoG-mediated myogenesis[86], and plays a hypoglycemic role by upregulating protein kinase C gamma (PKCγ) and cytosolic carboxypeptidase 1 (CCP-1) in diabetic rat proliferation[85]. Furthermore, it can also attenuate cognitive deficits and neuronal damage in diabetic rats by upregulating the expression of PKC γ and recombinant caveolin 1 (Cav-1)[87]. Loganin reduces high glucose-induced CTGF excretion in HK-2 cells through the ERK signaling pathway, and CTGF may be a potential target for treating diabetic nephropathy[88]. Morroniside can attenuate dysfunction of BMSC cells induced by high glucose through the activation of Glo1 and the inhibition of AGE-RAGE signaling. It may be a potential treatment target for both diabetes and osteoporosis[89]. Valerian iridoids inhibited the activity of mTORC1, thereby inducing autophagy and reducing hepatic lipid accumulation in mice caused by oleic acid (OA)[90]. Oleuropein inhibits aldose reductase and enhances rod and cone photoreceptors to protect retinal cells from the toxic effects of glucose[91]. Iridoids from *C. officinalis* and *Rehmannia glutinosa* ameliorated renal injury in C57BL/KsJ-db/db diabetic mice by inhibiting the AGEs/RAGE/sphingosine kinase 1 (SphK1) signaling pathway[92]. Genipin rapidly inhibits proton leakage mediated by uncoupling protein 2 (UCP2), which stimulates insulin secretion in a UCP2-dependent manner. Additionally, the acute addition of genipin to isolated islets reverses β-cell dysfunction caused by hyperglycemia and obesity[93].

3 Prospect

At present, the potential of natural products in new drug development has attracted the attention of an increasing number of scientists. Here, we summarize a series of iridoids represented by geniposide and catalpol, which have shown anti-diabetic, anti-inflammatory, and anti-oxidative effects through the PI3K, AMPK and NF-κB signaling pathways (Fig. 5). Therefore, iridoids represented by geniposide and catalpol show great potential in the treatment of diabetes and its complications, and are hopeful to be developed as clinical drugs.

4 Conclusions

Diabetes is a significant global public health problem[94], and an increasing number of active compounds from natural products have been idenified. Iridoids of plant origin have gained the attention of researchers due to their safety and wide range of biological activities. This review systematically summarized how the intervention of iridoid glycosides can reduce blood glucose and improve diabetes and its complications through different mechanisms. These include the inhibition of *α*-glucosidase, anti-inflammatory and antioxidant effects, inhibition of apoptosis and pyroptosis, enhancement of insulin sensitivity, promotion of glucose uptake and utilization, and regulation of intestinal flora. Iridoids can inhibit *α*-glucosidase activity and regulate enzymes related to glucose metabolism, such as PEPCK and G6Pase, in order to lower blood glucose levels. They also inhibit signaling pathways such as NF-κB, JNK/MAPK, and NLRP3 inflammasome, which helps to improve inflammation-related insulin resistance and tissue damage. Moreover, iridoids alleviate oxidative stress via ROS inhibition and signaling pathways such as ERK/MAPK, AGEs/RAGE/NOX4, and SIRT1/SIRT3-FOXO3a. They also improve insulin sensitivity and glucose metabolism

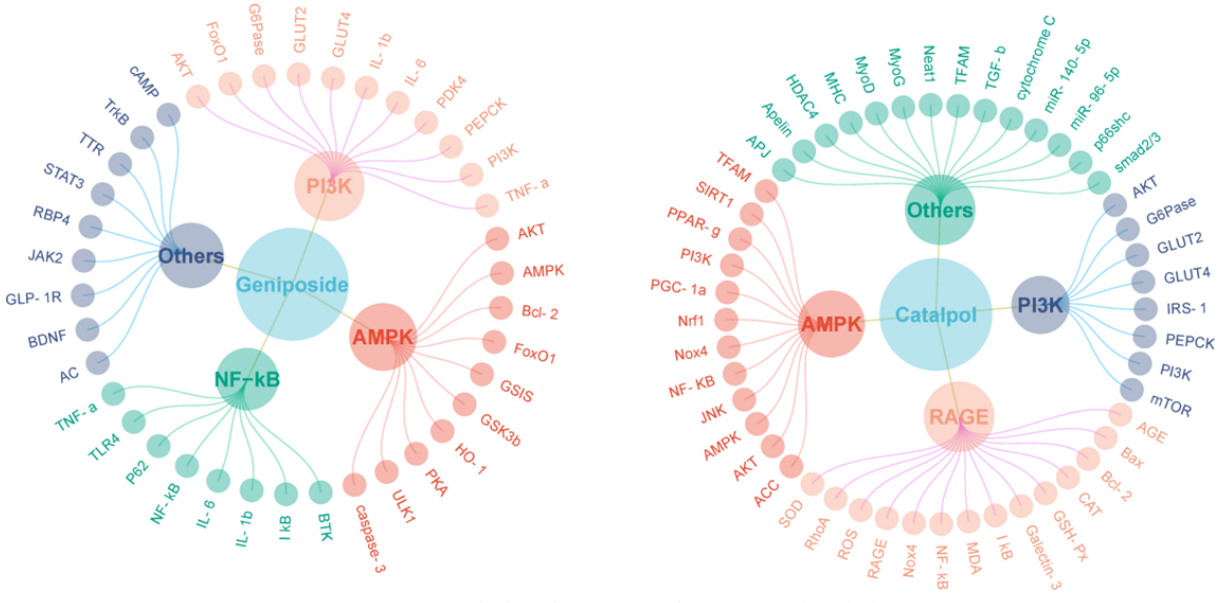


Figure 5 Network of signaling pathways of Geniposide and Catalpol.

through signaling pathways such as IRS-1/PI3K/AKT/GLUT4, AMPK/SIRT1/PGC-1α/PPAR-γ, and JNK/IRS-1/Akt/GSK3β. Furthermore, iridoids inhibit apoptosis and pyroptosis through signaling pathways such as ROS and AGEs/RAGE/p38MAPK. Additionally, they can alleviate insulin resistance and glucose metabolism dysfunction by increasing GLP-1 secretion, modulating the gut microbiota, and improving mitochondrial function. Overall, iridoids exhibit many beneficial effects on diabetes and its complications. The main molecular mechanisms involved are signaling pathways such as NF-κB, MAPK, AMPK, PI3K/AKT, NLRP3, ROS, NOX4, AGEs/RAGE, and others. This article reviews recent research on the mechanisms of iridoids in the treatment of diabetes and its complications, which will help to promote people's understanding of the application of iridoids in the treatment of diabetes and its complications and provides a theoretical basis for the development and application of iridoids in functional food and pharmaceutical industries.

However, despite extensive research on potential mechanisms and pathways, a comprehensive understanding of the molecular mechanisms through which iridoids regulate these pathways remains lacking. For example, while many studies focus on classical inflammatory signaling pathways such as NF-κB and MAPK to improve diabetes through anti-inflammatory effects, there has also been research on non-classical anti-inflammatory pathways or new targets for regulating inflammation[95,96]. Whether iridoid compounds can achieve a more optimal hypoglycemic effect through these new pathways is still worth exploring. Secondly, to gain a better understanding of the hypoglycemic effects of iridoids (cyclic enol ether terpenoids) in humans, it is imperative to conduct clinical studies that reflect real conditions within the human body.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

Acknowledgements

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References

[1] Wang, L., Meng, X. J., Zhou, H. H., et al. Iridoids and active ones in patrinia: A review. *Heliyon*, **2023**, 9: e16518. https://doi.org/10.1016/j.heliyon.2023.e16518

[2] Kong, Y. F., Yang, B., Hu, Y. L., et al. Research advance on structural modification and structure-activity relationship of iridoids. *Natural Product Research and Development*, **2021**, 33: 1236–1250. https://doi.org/10.16333/j.1001-6880.2021.7.019

[3] Jaafar, A., Zulkipli, M. A., Hatta, F. H. M., et al. Therapeutic potentials of iridoids derived from Rubiaceae against *in vitro* and *in vivo* inflammation: A scoping review. *Saudi Pharmaceutical Journal*, **2024**, 32: e101876. https://doi.org/10.1016/j.jsps.2023.101876

[4] Scicchitano, S., Vecchio, E., Battaglia, A. M., et al. The double-edged sword of oleuropein in Ovarian cancer cells: From antioxidant functions to cytotoxic effects. *International Journal of Molecular Sciences*, **2023**, 24: e842. https://doi.org/10.3390/ijms24010842

[5] Liu, J. X., Song, C. M., Nie, C. Z. P., et al. A novel regulatory mechanism of geniposide for improving glucose homeostasis mediated by circulating RBP4. *Phytomedicine*, **2022**, 95: e153862. https://doi.org/10.1016/j.phymed.2021.153862

[6] Liu, X. M., Hu, Y. T., Zhang, X., et al. Valtrate, an iridoid compound in *Valeriana*, elicits anti-glioblastoma activity through inhibition of the PDGFRA/MEK/ERK signaling pathway. *Journal of Translational Medicine*, **2023**, 21: e147. https://doi.org/10.1186/s12967-023-03984-0

[7] Li, N., Li, L., Wu, H. M., et al. Antioxidative property and molecular mechanisms underlying geniposide-mediated therapeutic effects in diabetes mellitus and cardiovascular disease. *Oxidative Medicine and Cellular Longevity*, **2019**, 2019: e7480512. https://doi.org/10.1155/2019/7480512

[8] Bhattamisra, S. K., Koh, H. M., Lim, S. Y., et al. Molecular and biochemical pathways of catalpol in alleviating diabetes mellitus and its complications. *Biomolecules*, **2021**, 11: e323. https://doi.org/10.3390/biom11020323

[9] Cheng, Y. C., Chiu, Y. M., Dai, Z. K., et al. Loganin ameliorates painful diabetic neuropathy by modulating oxidative stress, inflammation and insulin sensitivity in streptozotocin-nicotinamide-induced diabetic rats. *Cells*, **2021**, 10: e2688. https://doi.org/10.3390/cells10102688

[10] Zheng, S. J., Huang, K. L., Tong, T. Efficacy and mechanisms of oleuropein in mitigating diabetes and diabetes complication. *Journal of Agricultural and Food Chemistry*, **2021**, 69: 6145–6155. https://doi.org/10.1021/acs.jafc.1c01404

[11] Zaccardi, F., Webb, D. R., Yates, T., et al. Pathophysiology of type 1 and type 2 diabetes mellitus: A 90-year perspective. *Postgraduate Medical Journal*, **2016**, 92: 63–69. https://doi.org/10.1136/postgradmedj-2015-133281

[12] He, L. Y., Yang, F. Q., Tang, P., et al. Regulation of the intestinal flora: A potential mechanism of natural medicines in the treatment of type 2 diabetes mellitus. *Biomedicine & Pharmacotherapy*, **2022**, 151: e113091. https://doi.org/10.1016/j.biopha.2022.113091

[13] Everett, B. M., Donath, M. Y., Pradhan, A. D., et al. Anti-inflammatory therapy with Canakinumab for the prevention and management of diabetes. *Journal of the American College of Cardiology*, **2018**, 71: 2392–2401. https://doi.org/10.1016/j.jacc.2018.03.002

[14] Rehman, K., Akash, M. S. H. Mechanisms of inflammatory responses and development of insulin resistance: How are they interlinked. *Journal of Biomedical Science*, **2016**, 23: e87. https://doi.org/10.1186/s12929-016-0303-y

[15] Lontchi, Y. E., Sobngwi, E., Matsha, T. E., et al. Diabetes mellitus and inflammation. *Current Diabetes Reports*, **2013**, 13: 435–444. https://doi.org/10.1007/s11892-013-0375-y

[16] Yu, H., Lin, L. B., Zhang, Z. Q., et al. Targeting NF-κB pathway for the therapy of diseases: Mechanism and clinical study. *Signal Transduction and Targeted Therapy*, **2020**, 5: e209. https://doi.org/10.1038/s41392-020-00312-6

[17] Arthur, J. S. C., Ley, S. C. Mitogen-activated protein kinases in innate immunity. *Nature Reviews Immunology*, **2013**, 13: 679–692. https://doi.org/10.1038/nri3495

[18] Hsu, M. L., Huang, W. C., Zhou, Y. R., et al. Oleuropein protects human retinal pigment epithelium cells from IL-1β-induced inflammation by blocking MAPK/NF-κB signaling pathways. *Inflammation*, **2022**, 45: 297–307. https://doi.org/10.1007/s10753-021-01546-4

[19] Xu, L., Li, D. D., Zhu, Y. Q., et al. Swertiamarin supplementation prevents obesity-related chronic inflammation and insulin resistance in mice fed a high-fat diet. *Adipocyte*, **2021**, 10: 160–173. https://doi.org/10.1080/21623945.2021.1906510

[20] Wu, Q., Gai, S. K., Zhang, H. J. Asperulosidic acid, a bioactive iridoid, alleviates placental oxidative stress and inflammatory responses in gestational diabetes mellitus by suppressing NF-κB and MAPK signaling pathways. *Pharmacology*, **2022**, 107: 197–205. https://doi.org/10.1159/000521080

[21] Cui, X. R., Yu, Y., Yu, J., et al. Iridoid glycoside cornuside alleviates the symptom of gestational diabetes mellitus by suppressing inflammation and regulating beta cell function. *Gynecologic and Obstetric Investigation*, **2023**, 89: 59–68. https://

doi.org/10.1159/000534623
[22] Niu, D., Chen, X., Wang, T., et al. Protective effects of iridoid glycoside from *Corni Fructus* on type 2 diabetes with nonalcoholic fatty liver in mice. *Biomed Research International*, **2021**, 2021: e3642463. https://doi.org/10.1155/2021/3642463
[23] Ma, B., Zhu, Z. M., Zhang, J., et al. Aucubin alleviates diabetic nephropathy by inhibiting NF-κB activation and inducing SIRT1/SIRT3-FOXO3a signaling pathway in high-fat diet/streptozotocin-induced diabetic mice. *Journal of Functional Foods*, **2020**, 64: e103702. https://doi.org/10.1016/j.jff.2019.103702
[24] Zhou, J., Xu, G., Ma, S., et al. Catalpol ameliorates high-fat diet-induced insulin resistance and adipose tissue inflammation by suppressing the JNK and NF-κB pathways. *Biochemical and Biophysical Research Communications*, **2015**, 467: 853–858. https://doi.org/10.1016/j.bbrc.2015.10.054
[25] Chen, J., Yang, Y. W., Lv, Z. Y., et al. Study on the inhibitive effect of catalpol on diabetic nephropathy. *Life Sciences*, **2020**, 257: e118120. https://doi.org/10.1016/j.lfs.2020.118120
[26] Xiao, H. M., Sun, X. H., Liu, R. B., et al. Gentiopicroside activates the bile acid receptor Gpbar1 (TGR5) to repress NF-kappaB pathway and ameliorate diabetic nephropathy. *Pharmacological Research*, **2020**, 151: e104559. https://doi.org/10.1016/j.phrs.2019.104559
[27] Huang, Y., Xu, W., Zhou, R. B. NLRP3 inflammasome activation and cell death. *Cellular & Molecular Immunology*, **2021**, 18: 2114–2127. https://doi.org/10.1038/s41423-021-00740-6
[28] Komg, X. R., Zhao, Y. Y., Wang, X. Y., et al. Loganin reduces diabetic kidney injury by inhibiting the activation of NLRP3 inflammasome-mediated pyroptosis. *Chemico-Biological Interactions*, **2023**, 382: e110640. https://doi.org/10.1016/j.cbi.2023.110640
[29] Cheng, Y. C., Chu, L. W., Chen, J. Y., et al. Loganin attenuates high glucose-induced Schwann cells pyroptosis by inhibiting ROS generation and NLRP3 inflammasome activation. *Cells*, **2020**, 9: e1948. https://doi.org/10.3390/cells9091948
[30] Bao, X. W., Li, J. Q., Ren, C. X., et al. Aucubin ameliorates liver fibrosis and hepatic stellate cells activation in diabetic mice via inhibiting ER stress-mediated IRE1α/TXNIP/NLRP3 inflammasome through NOX4/ROS pathway. *Chemico-Biological Interactions*, **2022**, 365: e110074. https://doi.org/10.1016/j.cbi.2022.110074
[31] Wang, B., Yao, J., Yao, X., et al. Swertiamarin alleviates diabetic peripheral neuropathy in rats by suppressing NOXS/ ROS/NLRP3 signal pathway. *Journal of Southern Medical University*, **2021**, 41: 937–941. https://doi.org/10.12122/j.issn.1673-4254.2021.06.18
[32] Zou, X. Z., Zhang, Y. W., Pan, Z. F., et al. Gentiopicroside alleviates cardiac inflammation and fibrosis in T2DM rats through targeting Smad3 phosphorylation. *Phytomedicine*, **2022**, 106: e154389. https://doi.org/10.1016/j.phymed.2022.154389
[33] Fang, C. J., Rong, X. J., Jiang, W. W., et al. Geniposide promotes wound healing of skin ulcers in diabetic rats through PI3K/Akt pathway. *Heliyon*, **2023**, 9: e21331. https://doi.org/10.1016/j.heliyon.2023.e21331
[34] Chen, X. Y., Jiang, W. W., Liu, Y. L., et al. Anti-inflammatory action of geniposide promotes wound healing in diabetic rats. *Pharmaceutical Biology*, **2022**, 60: 294–299. https://doi.org/10.1080/13880209.2022.2030760
[35] Singh, A., Kukreti, R., Saso, L., et al. Mechanistic insight into oxidative stress-triggered signaling pathways and type 2 diabetes. *Molecules*, **2022**, 27: e950. https://doi.org/10.3390/molecules27030950
[36] Rani, V., Deep, G., Singh, R. K., et al. Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. *Life Sciences*, **2016**, 148: 183–193. https://doi.org/10.1016/j.lfs.2016.02.002
[37] Newsholme, P., Cruzat, V. F., Keane, K. N., et al. Molecular mechanisms of ROS production and oxidative stress in diabetes. *Biochemical Journal*, **2016**, 473: 4527–4550. https://doi.org/10.1042/BCJ20160503C
[38] Chen, Y. P., Jiao, N., Jiang, M., et al. Loganin alleviates testicular damage and germ cell apoptosis induced by AGEs upon diabetes mellitus by suppressing the RAGE/p38MAPK/NF-κB pathway. *Journal of Cellular and Molecular Medicine*, **2020**, 24: 6083–6095. https://doi.org/10.1111/jcmm.15198
[39] Chen, Y. P., Wu, Y. H., Gan, X. Y., et al. Iridoid glycoside from *Cornus officinalis* ameliorated diabetes mellitus-induced testicular damage in male rats: Involvement of suppression of the AGEs/RAGE/p38 MAPK signaling pathway. *Journal of Ethnopharmacology*, **2016**, 194: 850–860. https://doi.org/10.1016/j.jep.2016.10.079
[40] Jiao, N., Chen, Y. P., Zhu, Y. H., et al. Protective effects of catalpol on diabetes mellitus-induced male reproductive damage via suppression of the AGEs/RAGE/Nox4 signaling pathway. *Life Sciences*, **2020**, 256: e116736. https://doi.org/10.1016/j.lfs.2019.116736
[41] Yan, J. T., Wang, C. Y., Jin, Y., et al. Catalpol ameliorates hepatic insulin resistance in type 2 diabetes through acting on AMPK/NOX4/PI3K/AKT pathway. *Pharmacological Research*, **2018**, 130: 466–480. https://doi.org/10.1016/j.phrs.2017.12.026
[42] Zhang, Y. K., Wang, C. Y., Lu, J. W., et al. Targeting of miR-96-5p by catalpol ameliorates oxidative stress and hepatic steatosis in LDLr-/- mice via p66shc/cytochrome C cascade. *Aging-Us*, **2020**, 12: 2049–2069. https://doi.org/10.18632/aging.102721
[43] Dusabimana, T., Park, E. J., Je, J., et al. Geniposide improves diabetic nephropathy by enhancing ULK1-mediated autophagy and reducing oxidative stress through AMPK activation. *International Journal of Molecular Sciences*, **2021**, 22: e1651. https://doi.org/10.3390/ijms22041651
[44] Yang, Y., Li, J., Wei, C., et al. Amelioration of nonalcoholic fatty liver disease by swertiamarin in fructose-fed mice. *Phytomedicine*, **2019**, 59: e152782. https://doi.org/10.1016/j.phymed.2018.12.005
[45] Huang, X. J., Liu, G. H., Guo, J., et al. The PI3K/AKT pathway in obesity and type 2 diabetes. *International Journal of Biological Sciences*, **2018**, 14: 1483–1496. https://doi.org/10.7150/ijbs.27173
[46] Entezari, M., Hashemi, D., Taheriazam, A., et al. AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation. *Biomedicine & Pharmacotherapy*, **2022**, 146: e112563. https://doi.org/10.1016/j.biopha.2021.112563
[47] Sarma, P., Bharadwaj, S., Swargiary, D., et al. Iridoid glycoside isolated from *Wendlandia glabrata* and the role of its enriched fraction in regulating AMPK/PEPCK/G6Pase signaling pathway of hepatic gluconeogenesis. *New Journal of Chemistry*, **2022**, 46: 13167–13177. https://doi.org/10.1039/D1NJ05856H
[48] Yap, K. H., Yee, G. S., Candasamy, M., et al. Catalpol ameliorates insulin sensitivity and mitochondrial respiration in skeletal muscle of type-2 diabetic mice through insulin signaling pathway and AMPK/SIRT1/PGC-1α/PPAR-γ activation. *Biomolecules*, **2020**, 10: e1360. https://doi.org/10.3390/biom10101360
[49] Liu, J., Zhang, H. R , Hou, Y. B., et al. Global gene expression analysis in liver of db/db mice treated with catalpol. *Chinese Journal of Natural Medicines*, **2018**, 16: 590–598. https://doi.org/10.1016/S1875-5364(18)30096-7
[50] Xu, D. Q., Huang, X. F., Hassan, H. M., et al. Hypoglycaemic effect of catalpol in a mouse model of high-fat diet-induced prediabetes. *Applied Physiology Nutrition and Metabolism*, **2020**, 45: 1127–1137. https://doi.org/10.1139/apnm-2020-0075
[51] Kang, J. F., Guo, C., Thome, R., et al. Hypoglycemic, hypolipidemic and antioxidant effects of iridoid glycosides extracted from *Corni fructus*: possible involvement of the PI3K-Akt/PKB signaling pathway. *Rsc Advances*, **2018**, 8: 30539–30549. https://doi.org/10.1039/C8RA06045B
[52] Patel, T. P., Rawal, K., Soni, S., et al. Swertiamarin ameliorates oleic acid induced lipid accumulation and oxidative stress by attenuating gluconeogenesis and lipogenesis in hepatic steatosis. *Biomedicine & Pharmacotherapy*, **2016**, 83: 785–791. https://doi.org/10.1016/j.biopha.2016.07.028
[53] Liu, Z. H., Meng, L. J., Wang, M. K., et al. New iridoids from

Patrinia scabiosaefolia and their hypoglycemic effects by activating PI3K/Akt signaling pathway. *Fitoterapia*, **2023**, 165: e105423. https://doi.org/10.1016/j.fitote.2022.105423

[54] Sinha, K., Kumar, S., Rawat, B., et al. Kutkin, iridoid glycosides enriched fraction of *Picrorrhiza kurroa* promotes insulin sensitivity and enhances glucose uptake by activating PI3K/Akt signaling in 3T3-L1 adipocytes. *Phytomedicine : International Journal of Phytotherapy and PhytopharmaCology*, **2022**, 103: 154204. https://doi.org/10.1016/j.phymed.2022.154204

[55] Liu, Z. H., Xu, L. T., Xu, X. Q., et al. Effects and mechanisms of iridoid glycosides from *Patrinia scabiosaefolia* on improving insulin resistance in 3T3-L1 adipocytes. *Food and Chemical Toxicology*, **2019**, 134: e110806. https://doi.org/10.1016/j.fct.2019.110806

[56] Choi, E. M., Suh, K. S., Yun, S. J., et al. Oleuropein attenuates the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-perturbing effects on pancreatic β-cells. *Journal of Environmental Science and Health Part a-Toxic/Hazardous Substances & Environmental Engineering*, **2021**, 56: 752–761. https://doi.org/10.1080/10934529.2021.1923312

[57] Jiang, H. W., Ma, Y. J., Yan, J. Q., et al. Geniposide promotes autophagy to inhibit insulin resistance in HepG2 cells via P62/NF-κB/GLUT-4. *Molecular Medicine Reports*, **2017**, 16: 7237–7244. https://doi.org/10.3892/mmr.2017.7503

[58] Wei, J. J., Zhao, Y. T., Liang, H. H., et al. Preliminary evidence for the presence of multiple forms of cell death in diabetes cardiomyopathy. *Acta Pharmaceutica Sinica B*, **2022**, 12: 1–17. https://doi.org/10.1016/j.apsb.2021.08.026

[59] Kim, S., Kang, S. W., Joo, J., et al. Characterization of ferroptosis in kidney tubular cell death under diabetic conditions. *Cell Death & Disease*, **2021**, 12: e382. https://doi.org/10.1038/s41419-021-03452-x

[60] Liu, Y., Dai, W., Ye, S. D. The olive constituent oleuropein exerts nephritic protective effects on diabetic nephropathy in *db/db* mice. *Archives of Physiology and Biochemistry*, **2019**, 128: 455–462. https://doi.org/10.1080/13813455.2019.1691603

[61] Mclean, B. A., Wong, C. K., Campbell, J. E., et al. Revisiting the complexity of GLP-1 action from sites of synthesis to receptor activation. *Endocrine Reviews*, **2021**, 42: 101–132. https://doi.org/10.1210/endrev/bnab024

[62] Mueller, T. D., Finan, B., Bloom, S. R., et al. Glucagon-like peptide 1 (GLP-1). *Molecular Metabolism*, **2019**, 30: 72–130. https://doi.org/10.1016/j.molmet.2019.09.010

[63] Drucker, D. J. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metabolism*, **2018**, 27: 740–756. https://doi.org/10.1016/j.cmet.2018.03.001

[64] Del, B. M., Nocella, C., Loffreddo, L., et al. Oleuropein-enriched chocolate by extra virgin olive oil blunts hyperglycaemia in diabetic patients: Results from a one-time 2-hour post-prandial cross over study. *Clinical Nutrition*, **2020**, 39: 2187–2191. https://doi.org/10.1016/j.clnu.2019.09.006

[65] Suh, H. W., Lee, K. B., Kim, K. S., et al. A bitter herbal medicine *Gentiana scabra* root extract stimulates glucagon-like peptide-1 secretion and regulates blood glucose in *db/db* mouse. *Journal of Ethnopharmacology*, **2015**, 172: 219–226. https://doi.org/10.1016/j.jep.2015.06.042

[66] Lin, L. C., Lee, L. C., Huang, C., et al. Effects of boschnaloside from *Boschniakia rossica* on dysglycemia and islet dysfunction in severely diabetic mice through modulating the action of glucagon-like peptide-1. *Phytomedicine*, **2019**, 62: e152946. https://doi.org/10.1016/j.phymed.2019.152946

[67] Mishra, S. P., Wang, B., Jain, S., et al. A mechanism by which gut microbiota elevates permeability and inflammation in obese/diabetic mice and human gut. *Gut*, **2023**, 72: 1848–1865. https://doi.org/10.1136/gutjnl-2022-327365

[68] Yang, G., Wei, J. L., Liu, P. Y., et al. Role of the gut microbiota in type 2 diabetes and related diseases. *Metabolism-Clinical and Experimental*, **2021**, 117: e154712. https://doi.org/10.1016/j.metabol.2021.154712

[69] Cunningham, A. L., Stephens, J. W., Harris, D. A. Gut microbiota influence in type 2 diabetes mellitus (T2DM). *Gut Pathogens*, **2021**, 13: e50. https://doi.org/10.1186/s13099-021-00446-0

[70] Zheng, S. J., Wang, Y. A., Fang, J. J., et al. Oleuropein ameliorates advanced stage of type 2 diabetes in *db/db* mice by regulating gut microbiota. *Nutrients*, **2021**, 13: e2131. https://doi.org/10.3390/nu13072131

[71] Nakamura, A., Yokoyama, Y., Tanaka, K., et al. Asperuloside improves obesity and type 2 diabetes through modulation of gut microbiota and metabolic signaling. *Iscience*, **2020**, 23: e101522. https://doi.org/10.1016/j.isci.2020.101522

[72] Niu, D., An, S. J., Chen, X., et al. *Corni Fructus* as a natural resource can treat type 2 diabetes by regulating gut microbiota. *American Journal of Chinese Medicine*, **2020**, 48: 1385–1407. https://doi.org/10.1142/S0192415X20500688

[73] Zhu, Y. H., Du, Q., Jiao, N., et al. Catalpol ameliorates diabetes-induced testicular injury and modulates gut microbiota. *Life Sciences*, **2021**, 267: e118881. https://doi.org/10.1016/j.lfs.2020.118881

[74] Zengin, G., El-Raey, M., El-Kashak, W., et al. Sweroside: An iridoid glycoside of potential neuroprotective, antidiabetic, and antioxidant activities supported by molecular docking. *Amino Acids*, **2023**, 55: 1765–1774. https://doi.org/10.1007/s00726-023-03262-9

[75] Vajravijayan, S., Nandhagopal, N., Anantha, K. D. A., et al. Isolation and characterization of an iridoid, arbortristoside-C from *Nyctanthes arbor* tristis Linn., a potential drug candidate for diabetes targeting α-glucosidase. *Journal of Biomolecular Structure & Dynamics*, **2022**, 40: 337–347. https://doi.org/10.1080/07391102.2020.1813201

[76] Ye, X. S., He, J., Xu, J. K., et al. Undescribed morroniside-like secoiridoid diglycosides with *α*-glucosidase inhibitory activity from *Corni Fructus*. *Phytochemistry*, **2020**, 171: e112232. https://doi.org/10.1016/j.phytochem.2019.112232

[77] He, K., Song, S. H., Zou, Z. Y., et al. The hypoglycemic and synergistic effect of loganin, morroniside, and ursolic acid isolated from the fruits of *Cornus officinalis*. *Phytotherapy Research*, **2016**, 302: 283–291. https://doi.org/10.1002/ptr.5529

[78] Yang, X. L., Wang, Y. J., Tang, X. Q., et al. *Corni Fructus* extracts ameliorate streptozotocin-induced diabetes in mice via regulating AMPK/ACC/CPT-1 signaling pathway. *Journal of Functional Foods*, **2023**, 107: e105661. https://doi.org/10.1016/j.jff.2023.105661

[79] Shu, A. M., Du, Q., Chen, J., et al. Catalpol ameliorates endothelial dysfunction and inflammation in diabetic nephropathy via suppression of RAGE/RhoA/ROCK signaling pathway. *Chemico-Biological Interactions*, **2021**, 348: e109625. https://doi.org/10.1016/j.cbi.2021.109625

[80] Sun, W. X., Gao, Y. Y., Cao, Y., et al. Catalpol prevents glomerular angiogenesis induced by advanced glycation end products via inhibiting galectin-3. *Current Medical Science*, **2023**, 43: 668–678. https://doi.org/10.1007/s11596-023-2750-5

[81] Yang, S. S., Deng, H. C., Zhang, Q. Z., et al. Amelioration of diabetic mouse nephropathy by catalpol correlates with down-regulation of Grb10 expression and activation of insulin-like growth factor 1/insulin-like growth factor 1 receptor signaling. *Plos One*, **2016**, 11: e0151857. https://doi.org/10.1371/journal.pone.0151857

[82] Dong, Z., Chen, C. X. Effect of catalpol on diabetic nephropathy in rats. *Phytomedicine*, **2013**, 20: 1023–1029. https://doi.org/10.1016/j.phymed.2013.04.007

[83] Chen, Y., Liu, Q. P., Shen, Z. F., et al. Catalpol ameliorates podocyte injury by stabilizing cytoskeleton and enhancing autophagy in diabetic nephropathy. *Frontiers in Pharmacology*, **2019**, 10: e1477. https://doi.org/10.3389/fphar.2019.01477

[84] Zou, G. L., Zhong, W. L., Wu, F., et al. Catalpol attenuates cardiomyocyte apoptosis in diabetic cardiomyopathy via Neat1/miR-140-5p/HDAC4 axis. *Biochimie*, **2019**, 165: 90–99. https://doi.org/10.1016/j.biochi.2019.05.005

[85] Lin, C. M., Wang, B. W., Fang, W. J., et al. Catalpol ameliorates neointimal hyperplasia in diabetic rats. *Planta Medica*, **2019**, 85: 406–411. https://doi.org/10.1055/a-0818-3689

[86] Xu, D. Q., Wang, L., Jiang, Z. Z., et al. A new hypoglycemic mechanism of catalpol revealed by enhancing MyoD/MyoG-mediated myogenesis. *Life Sciences*, **2018**, 209: 313–323. https://doi.org/10.1016/j.lfs.2018.08.028

[87] Zhou, H. C., Liu, J., Ren, L. Y., et al. Relationship with spatial memory in diabetic rats and protein kinase Cγ, caveolin-1 in the hippocampus and neuroprotective effect of catalpol. *Chinese Medical Journal*, **2014**, 127: 916–923. https://doi.org/10.3760/cma.j.issn.0366-6999.20132137

[88] Jiang, W. L., Zhang, S. P., Hou, J., et al. Effect of loganin on experimental diabetic nephropathy. *Phytomedicine*, **2012**, 19: 217–222. https://doi.org/10.1016/j.phymed.2011.08.064

[89] Sun, Y., Zhu, Y., Liu, X. Z., et al. Morroniside attenuates high glucose-induced BMSC dysfunction by regulating the Glo1/AGE/RAGE axis. *Cell Proliferation*, **2020**, 53: e12866. https://doi.org/10.1111/cpr.12866

[90] Lee, D. H., Park, S. H., Huh, Y. H., et al. Iridoids of *Valeriana fauriei* contribute to alleviating hepatic steatosis in obese mice by lipophagy. *Biomedicine & Pharmacotherapy*, **2020**, 125: e109950. https://doi.org/10.1016/j.biopha.2020.109950

[91] Benlarbi, M., Jemai, H., Hajri, K., et al. Neuroprotective effects of oleuropein on retina photoreceptors cells primary culture and olive leaf extract and oleuropein inhibitory effects on aldose reductase in a diabetic model: *Meriones shawi*. *Archives of Physiology and Biochemistry*, **2022**, 128: 593–600. https://doi.org/10.1080/13813455.2019.1708119

[92] Lv, X., Dai, G. Y., Lv, G. H., et al. Synergistic interaction of effective parts in *Rehmanniae Radix* and *Corpus officinalis* ameliorates renal injury in C57BL/KsJ-db/db diabetic mice: Involvement of suppression of AGEs/RAGE/SphK1 signaling pathway. *Journal of Ethnopharmacology*, **2016**, 185: 110–119. https://doi.org/10.1016/j.jep.2016.03.017

[93] Zhang, C. Y., Parton, L. E., Ye, C. P., et al. Genipin inhibits UCP2-mediated proton leak and acutely reverses obesity- and high glucose-induced β cell dysfunction in isolated pancreatic islets. *Cell Metabolism*, **2006**, 3: 417–427. https://doi.org/10.1016/j.cmet.2006.04.010

[94] Hwang, B. F., Sarasmita, M. A., Li, M. C., et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: A systematic analysis for the global burden of disease study 2021. *Lancet*, **2023**, 402: 203–234. https://doi.org/10.1016/S0140-6736(23)02044-5

[95] Wei, W., Zeng, Q. X., Wang, Y., et al. Discovery and identification of EIF2AK2 as a direct key target of berberine for anti-inflammatory effects. *Acta Pharm Sin B*, **2023**, 13: 2138–2151. https://doi.org/10.1016/j.apsb.2022.12.009

[96] Qiao, L., Ma, J., Zhang, Z. H., et al. Deficient chaperone-mediated autophagy promotes inflammation and atherosclerosis. *Circulation Research*, **2021**, 129: 1141–1157. https://doi.org/10.1161/CIRCRESAHA.121.318908