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REVIEW

The Beneficial Effects of Geniposide on Glucose and Lipid Metabolism: A Review

Siting Gao[1–3], Qin Feng[1–3]

[1]Institute of Liver Diseases, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Hepatopathy Building, Shanghai, People's Republic of China; [2]Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [3]Key Laboratory of Liver and Kidney Diseases, Ministry of Education, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China

Correspondence: Qin Feng, Institute of Liver Diseases, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 1200 Zhangheng Road, Pudong District, Shanghai, People's Republic of China, Tel +86 13764380682, Fax +86 021-51322043, Email fengqin@shutcm.edu.cn

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Abstract: Geniposide is a naturally sourced active ingredient that has diverse pharmacological effects and great potential in improving or treating different kinds of diseases. In recent years, more and more studies have confirmed that geniposide can improve glucose and lipid metabolism disorder, which is an increasingly prevalent health problem causing various metabolic diseases globally. Our review aims to summarize basic information on the pharmacological effects of geniposide on glucolipid metabolism. Geniposide increases glucose utilization and insulin production, protects pancreatic islet β cells, inhibits insulin resistance and hepatic glucose production, and suppresses gluconeogenesis. While in the aspect of lipid metabolism, geniposide can promote lipolysis, inhibit lipogenesis, and regulate lipid transport. Geniposide ameliorates lipid and glucose metabolic disorders, improving the entire glycolipid metabolism network in a three-dimensional manner at the level of molecular mechanism. Growing evidence revealed that geniposide may serve as an effective drug to combat metabolic diseases for the time to come.

Keywords: geniposide, lipid metabolism, glucose metabolism, Gardenia Jasminoides Ellis, metabolic disease, glucolipid metabolism, naturally sourced active ingredient, pharmacological evidence

Introduction

Glucose and lipid metabolism imbalance is a high-risk etiology leading to various complications, including obesity, diabetes, hyperlipemia, non-alcohol fatty liver disease (NAFLD), and cardiovascular diseases.[1] We are currently in the midst of a global metabolic disease epidemic, with its prevalence increasing with age.[2,3] There has been an increasing interest in investigating effective strategies to control and treat comorbidities associated with glucose and lipid metabolism disorders.[4] A variety of plants and natural active ingredients derived from plants have been used to combat diseases associated with glycolipid metabolism disorders.[5] Geniposide is one such naturally active ingredient derived from the fruits of Gardenia Jasminoides Ellis (GJE, popularly called Zhizi in China) and has traditionally been commonly used for hundreds of years in traditional Chinese medicine.[6]

There is an increasing number of pharmacological evidence proving that geniposide exerts various biological activities, including neuroprotective, antidiabetic, hepatoprotective, anti-inflammatory, analgesic, antidepressant-like, cardioprotective, antioxidant, immune-regulatory, antithrombotic, and anti-tumoral effects.[7–11] The anti-inflammatory, hepatoprotective, antidiabetic, and antioxidant properties of geniposide were reviewed before.[9,10,12–15] The most recognized pharmacological effects of geniposide are anti-inflammatory and antioxidant effects;[9,13] however, in recent years, a growing number of studies explored the role of geniposide in regulating glucolipid metabolism. How geniposide regulates the glucolipid metabolism, the specific mechanism, the disadvantages and future research directions have not been elucidated. There are few reviews on the improvement of glucolipid metabolism disorders and metabolic diseases using geniposide. As a consequence, a comprehensive review focusing on geniposide-regulated glucolipid metabolism is necessary to advance the knowledge on geniposide. This review will

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serve as a reference for researchers to further understand the pharmacological effects of geniposide and develop more valuable applications in the future.

Geniposide at a Glance

Structure and Physicochemical Properties

Geniposide (methyl (1S,4aS,7aS)-1-(β-D-glucopyranosyloxy)-7-(hydroxylmethyl)-1,4a,5,7a-tetrahydrocyclopenta[c]pyran-4-carboxylate; C17H24O10) is regarded as an iridoid glycoside, namely genipin 1-O-β-D-glucopyranoside (Figure 1).[10] From another perspective, geniposide is also regarded as a C11 methyl ester of geniposidic acid. Its molecular weight is 388,366. Because of its chemical structure, it is also considered a glycoside containing one molecule of genipin and glucose. Geniposide is a white or pale yellow powder with a density of 1.49 g/cm^3 and a melting point of 161.53°C.[7] It is easily dissolved in water, soluble in ethanol, and undissolved in petroleum ether.[6]

Sources

Geniposide is mainly sourced from GJE, but it is also detected in other commonly used Chinese herbal medicines, such as Eucommia Ulmoides Oliv (EUO), Rehmannia Officinalis (RO), and Radix Scrophulariae (RS) (Figure 2).[16] Among these, GJE contains about 3.3–8.56% geniposide, while RO only contains 0.205–0.4381%, EUO contains 0.0173–0.5811%, and RS contains 0.0699–0.1135% of geniposide. Therefore, GJE is the main geniposide source.[17] The 2015 edition of the Chinese Pharmacopoeia stipulates that geniposide abundance in GJE is no less than 1.8%. Geniposide content in GJE on the market reaches 6%.[18]

Pharmacokinetics

We investigated that the concentration of geniposide reached a peak in the liver and spleen 30 min after oral administration, and was detected in the kidney and brain 2 h later.[19] The absolute bioavailability of geniposide was 9.67% after it was metabolized within 12 h. The bioavailability of geniposide is strongly linked to different administration methods. In addition, geniposide can be converted to genipin by an intestinal microbiota enzyme (β-glucosidase) (Figure 3). Geniposide metabolism involves methylation, glucosylation, decarboxylation, taurine conjugation, hydrolysis, demethylation, hydrogenation, hydroxylation, cysteine S-conjugation through dehydration, sulfate conjugation, and other related complex reactions.[20,21] Geniposide is mainly excreted in its original form through the kidneys. The excretion level accounts for a proportion of over 90% of the initial dosage after 10 h.[22]

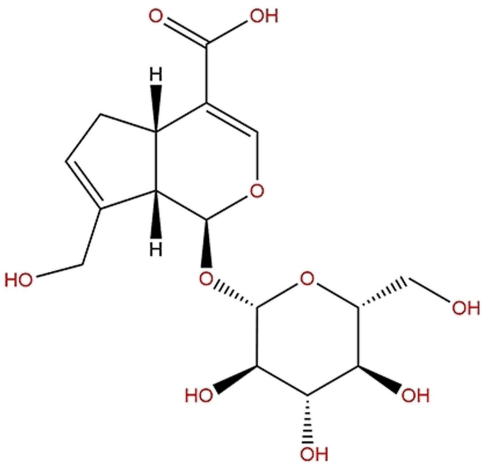

Figure 1 Chemical structure of geniposide.

Figure 2 Main sources of geniposide. (**A**). Gardenia Jasminoides Ellis (**B**). Eucommia Ulmoides Oliv (EUO) (**C**). Rehmannia Officinalis (RO) (**D**). Radix Scrophulariae (RS).

Main Pharmacological Functions of Geniposide

Geniposide exerts abundant and complicated pharmacological effects, such as anti-inflammatory, antioxidant, hepatoprotective, neuroprotective, analgesic, antidiabetic, antidepressant-like, immune-regulatory, cardioprotective, antithrombotic, and antitumoral effects.[8] These pharmacological effects have laid a foundation for its application in the improvement of a variety of diseases, such as cardiovascular diseases, diabetes and diabetic complications, hepatic diseases, Parkinson's disease, Alzheimer's disease, and ischemia and reperfusion injury. Some of the potential benefits include the influence on the normal and healthy operation of the nervous, endocrine, circulatory, digestive, urinary, muscle, and other different bodily systems.

In particular, the anti-inflammatory and antioxidant effects of geniposide have been widely studied. Geniposide not only fights inflammation-related diseases like swelling, pain, liver disease, Alzheimer's disease, and others but also inhibits classic inflammatory-related pathways such as NF-κB, MAPK, and TLR4 signaling pathways.[10] Geniposide could delay cell injury via upregulating endogenous antioxidative enzymes. Geniposide can also increase the activity of some important antioxidant enzymes and pathways including hepatic lipid peroxidation (LPO), glutathione-S-transferase (GST), glutathione (GSH), glutathione peroxidase (GPx), and copper- and zinc-containing superoxide dismutase (CuZn-SOD), and protects against oxidative stress injury.[23–25]

Pharmacological Effects of Geniposide in Glucose and Lipid Metabolism

Effects on Glucose Metabolism

It is well-known that an imbalanced glucose metabolism triggers many metabolic diseases. An adequate blood glucose level must be maintained at all time. Sources of blood glucose are intestinal absorption, liver glycogenolysis, and gluconeogenesis.[26] Glucose-consuming pathways include glucose uptake by various tissues and organs for oxidation, glycogen synthesis, and conversion into other sugars, fats, or amino acids. The balance of blood glucose is mainly regulated by hormones, including insulin, glucagon, adrenaline, and glucocorticoid.[27] The interaction between major glucose metabolic pathways, such as glycolysis, gluconeogenesis, glycogenesis, and glycogenolysis, maintains the homeostasis of hepatic glucose metabolism.[28] Figure 4 summarizes the pharmacological effects of geniposide on glucose metabolism and the details are exhibited in Table 1.

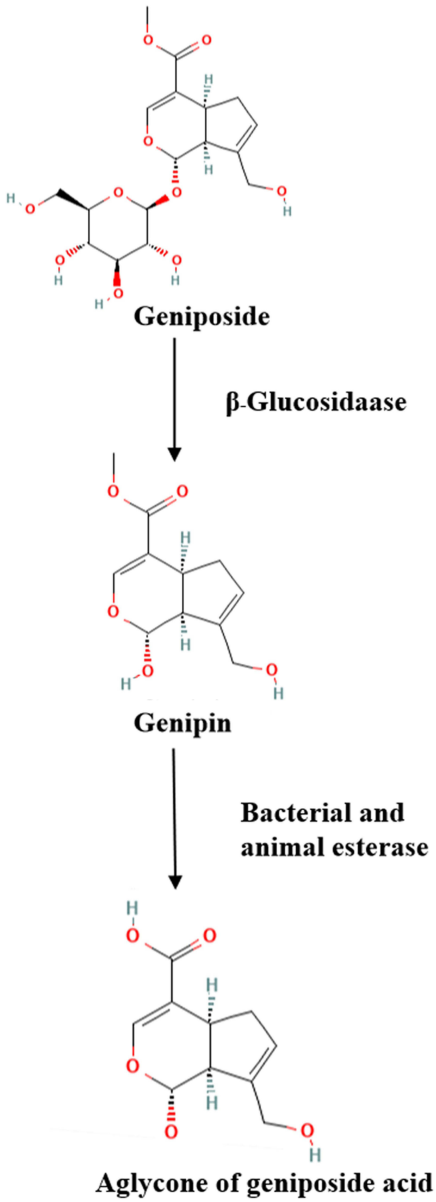

Figure 3 Schematic diagram of the metabolic effect of geniposide by β-glucosidase and esterase.

Increasing Glucose Utilization

Skeletal muscle, which is the main organ participating in the uptake and metabolism of glucose, contains slow-twitch and fast-twitch muscle fibers. Fast-twitch fibers generate adenosine triphosphate (ATP) primarily through glycolysis, whereas slow-twitch myofibers rich in mitochondria have high oxidative capacity.[29] Geniposide improves glucose homeostasis by promoting a slow-to-fast myofiber switch and glucose utilization. Further studies exposed that geniposide exerts the above effects by regulating forkhead box O1 (FoxO1)/ pyruvate dehydrogenase kinase 4 (PDK4), which controls respiratory substrate selection through pyruvate dehydrogenase.[30] From another point of view, in a 2022 study, it was revealed that geniposide regulates respiratory substrate selection, promotes glucose uptake in skeletal muscles, and suppresses glycogen storage by disturbing the synthesis, secretion, and homeostasis of retinol-binding protein 4 (RBP4).[31]

Increasing Insulin Production

Glucose-stimulated insulin secretion (GSIS) is essential to the maintenance of a stable level of blood glucose.[32] Guo et al[33] first reported that geniposide could increase GSIS, and the results indicated that glucagon-like peptide 1 receptors

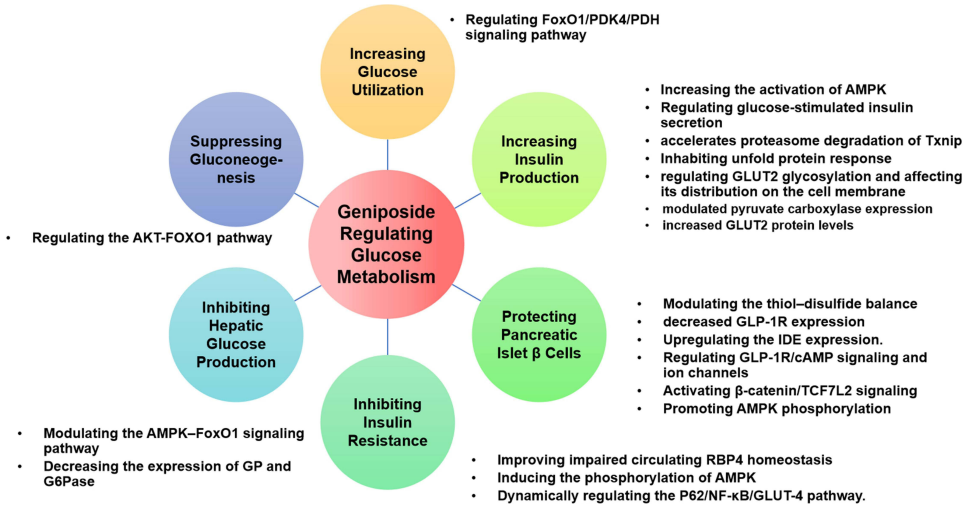

Figure 4 Pharmacological effects of geniposide on Glucose Metabolism.

(GLP-1R) plays an important role in the geniposide-regulated GSIS. Geniposide regulates GSIS possibly via pyruvate carboxylase-mediated glucose metabolism in pancreatic β cells.[34] Exploration from another point of view revealed that GSIS is phosphatidylinositol 3 kinase- dependent and geniposide increases the expression of glucose transporter 2 (GLUT2) in total cell lysates under normal glucose conditions.[35] An in-depth study focusing on GLUT2, indicated that it may be related to the regulation of glucosaminyl (N-acetyl) transferase family member 7 (GNT-IVa)-mediated glycosylation of GLUT2 and the residence of glycosylated GLUT2 on the pancreatic β cell membrane.[36] A 2021 study found that 5'AMP-activated protein kinase (AMPK) activation also plays an essential role in geniposide-regulated GSIS in pancreatic β cells.[37]

Protecting Pancreatic Islet β Cells

Diabetes is characterized by pancreatic islet β cell dysfunction or loss. One therapeutic strategy for improving blood glucose homeostasis is to prevent pancreatic islet β cells from failure and promote new pancreatic islet β cell formation.[27]

Geniposide is a promising pancreatic islet β cell protector, which prevents pancreatic islet β cells from exhaustion and injury resulting from excessive insulin secretion under high glucose conditions. Geniposide administration is a possible way of balancing the oxidative stress of pancreatic β cells by regulating the expression of protein disulfide isomerase (PDI) and endoplasmic reticulum oxidoreductin 1 (ERO1).[38] Extensive islet amyloid polypeptide (IAPP) deposits are thought to contribute to pancreatic β cell dysfunction, either by direct cytotoxicity or by reducing the pancreatic islet β cell mass, resulting in impaired insulin secretion. Geniposide prevents human IAPP-induced cytotoxicity in INS-1E cells through the upregulation of (insulin degrading enzyme) IDE.[39] Liu et al[40] suggested that AMPK plays a crucial role in how geniposide antagonizes high glucose-induced pancreatic β cell injury.

Elevated thioredoxin-interacting protein (Txnip) levels induce β cell apoptosis and dysfunction.[41] Geniposide improves GSIS by accelerating Txnip degradation. A further study proved that geniposide-related Txnip degradation attenuates the early-stage apoptosis of pancreatic β cells. Geniposide regulates Txnip degradation and GSIS through endoplasmic reticulum (ER) stress by accelerating the phosphorylation of Protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) and Inositol-requiring enzyme-1α (IRE1α).[42]

The main roles of GLP-1R are stimulation of GSIS, induction of pancreatic β-cell proliferation, inhibition of postprandial glucagon release, and delay in gastric emptying.[43] Geniposide inhibits the early stage of lipotoxicity-induced β-cell apoptosis, and GLP-1R plays a critical role by counteracting lipotoxicity in INS-1 pancreatic islet β cells.[44] Cui et al[45] analyzed the microarray data of INS-1 cells treated with geniposide and identified key lncRNAs and mRNAs in a 2021 study. They found that the lncRNA NONRATT027738 interacts with all three hub mRNAs (*Pomc, Htr2a*, and *Agtr1a*). There is also other research focusing on the role of GLP-1R in the beneficial effects of geniposide-

Table 1 In vivo/In vitro Studies of Geniposide in Glucose Metabolism

Effect on Glucose Metabolism	In vivo/In vitro	Model	Dose and Duration	Experimental Outcome	References
Increasing the Utilization of glucose	In vivo	C57BL/6 wild-type mice were fed a high-fat diet for 9 weeks	Geniposide 25mg/kg for 1 week	↑glucose utilization ↑fast-twitch muscle phenotype ↓the mRNA/protein levels of PDK4 in skeletal muscle ↓the mRNA/protein levels of FoxO1/PDK4/p-PDH/GAS	[30]
	In Vitro	Mouse C2C12 myoblasts treated with 2% horse serum to replace FBS in culure medium for 48 h	Geniposide 0.4mg/mL for 12 h	↑glucose utilization ↑fast-twitch muscle phenotype ↓the mRNA/protein levels of FoxO1/PDK4/p-PDH/GAS	[30]
Increasing Insulin Production	In Vitro	Rat INS-1 insulinoma cells exposed to 10 mol/L geniposide for 1 h	Geniposide 0.01/0.1/1/10/100μM for 1 h	↑insulin secretion ↑glucose-stimulated insulin secretion	[33]
		Rat INS-1 pancreatic β cell exposed to 5.5,11,33 mM glucose for 20 min	Geniposide 10μM for 2 h	↑insulin secretion ↑glucose uptake ↓content of ATP ↓the mRNA and protein levels of pyruvate carboxylase gene	[34]
		Rat INS-1 pancreatic β cell exposed to 5.5 mM glucose for 1 h	Geniposide 10μM for 1 h	↑the phosphorylation of PDK1 ↑the phosphorylation of Akt473 and GSK3β ↑the protein level of Glut2	[35]
		INS-1 pancreatic β cell exposed to 5/11/25 mmol/l glucose for 1 h	Geniposide 10μM for 2 h	↑the glycosylation of Glut2 ↑the mRNA and protein levels of GnT-IVa, galectin-9, clathrin	[36]
		INS-1 pancreatic β cell exposed to 5/25 mM glucose for 1 h	Geniposide 10 μM for 2 h	↑insulin secretion and ATP content ↓glucose uptake ↑ACC phosphorylation	[37]

Protecting Pancreatic Islet β Cells	In Vitro	INS-1 pancreatic β cell exposed to 5/11/25 mM glucose for 24 h	Geniposide 10 μM for 1 h	↑Insulin serection ↓The accumulation of H2O2 ↑the protein levels of protein disulfide isomerase ↓the protein levels of endoplasmic reticulum oxidoreductin 1 (ERO1) ↓the content of thiol group in INS-1 cells.	[38]
		Rat INS-1E insulinoma cell were incubated with 2.0 and 5.0 μM HIAPP	Geniposide 1.0/10/100μm for 2 h	↑cell viability ↑the proten levels of insulin-degrading enzyme ↑the aggregation of HIAPP	[39]
		INS-1 pancreatic β cell incubated5/11/25 mM glucose for 24.48 or 72 h	Geniposide 10μm for 5 minutes, 24 h, 48 h, and 72 h	↓glucose-induced impairment of insulin release ↑the phosphorylation of AMPK ↓the protein levels of HO-1 ↑the Bcl-2/BAX protein ratio ↑the cleavage of Caspase-3	[40]
		INS-1 pancreatic β cell exposed to 16.7 mM glucose/0.2mM palmitate for 24 h	Geniposide 10 μM for 24 h	↑cell viability ↑the protein expression of HO-1, Bcl-2 ↓the protein expression of Bax ↑PERK/eIF2α/IRE1α phosphorylation (Unfolded protein response)	[40]
		INS-1 pancreatic β cell exposed to 25 mM glucose for 24 h	Geniposide 10 μM for 24 h	↓ protein levels of Txnip ↓Insulin serection ↑glucose and ATP content	[41]
		INS-1 pancreatic β cell exposed to 25mM glucose for 12 h	Geniposide 10 μM for 2 h	↓PERK/eIF2α/IRE1α phosphorylation (Unfolded protein response)	[42]
		INS-1 rat insulinoma cell were incubated with palmitate for 18 h	Geniposide 1μm for 2 h	↓palmitate-induced cell apoptosis ↓the protein levels of caspase-3 ↓the phosphorylation of Akt (Thr308), Akt (ser473) and Foxo1 ↓the protein levels of PDX-1	[44]
		Rat Islets cells were stimulated with 2.8 mM or 8.3 mM glucose for 0.5 h	Geniposide 10μm for 0.5 h	↑insulin secretion ↑cAMP accumulation ↓ Kv channels ↑action potential duration ↑currents through voltage-dependent Ca^2 channels	[39]
	In vivo	C57BL/6 male mice were fed a high-fat diet for 12 weeks	Geniposide solution was prepared in 0.9% NaCl and delivered by oral gavage at dosage of 100 mg/kg daily	↓pancreatic islet β cell apoptosis ↑the protein and mRNA levels of TCF7L2 ↑the mRNA levels of insulin,PDX1,IL1β, and CyclinD1 ↑β-catenin/TCF7L2 signaling ↑β-cell regeneration	[46]

(*Continued*)

Table 1 (Continued).

Effect on Glucose Metabolism	In vivo/In vitro	Model	Dose and Duration	Experimental Outcome	References
Inhibiting Insulin Resistance	In vivo	Spontaneously obese Type 2 diabetic (TSOD) mices	0.1%/0.3% geniposide for 8 weeks	↓Plasma Glucose levels in Oral Glucose Tolerance Test	[47]
		Male C57BL/6 J mice fed with High-Fat Diet for 8 weeks	Geniposde 25 or 50 mg/kg for 8 weeks	↓the body weight gain ↓the random blood glucose and fasting blood glucose levels ↓the area under the curve of glucose tolerance tests and insulin tolerance tests ↓hepatic glycogen content and serum insulin ↑the phosphorylations of hepatic IR, Akt (S473) and GSK3β in liver and GAS ↓the mRNA/protein levels of FoxO1 and PDK4 ↑the mRNA levels and protein levels of Glut4 ↓serum RBP4 levels and the mRNA/protein levels of RBP4 and TTR	[31]
	In Vitro	3T3-L1 adipocyte cells cultured with 33 mM glucose and 100 nM insulin for 48 h	Geniposide 10μm for 2 h	↑Glucose uptake ↓the protein levels of p-IRS-1, IRS-1, GLUT −1, and IR-β ↑Txnip deregulation ↑the phosphorylation of AMPK	[49]
		HepG2 cell treated with 50, 100, 200 or 500 nmol/l insulin for 48h	Geniposide 62.5 mg/l for 20 h	↓supernatant glucose centent ↑the mRNA and protein levels of Glut4 ↑Autophagy (↑the protein levels of LC3,P62) ↑the protein levels of P62,P65	[48]
		Primary mouse hepatocytes were isolated from the C57BL/6 J mice	Geniposide 50 mg/l for 24 h	↓the mRNA/protein levels of RBP4 and TTR ↓RBP4 levels in the culture medium	[31]

Inhibiting Hepatic Glucose Production	In Vitro	HepG2 treated with 5.5mM D-glucose	Geniposide 0.1/1/10/100μm for 6 h	↓Glucose production ↑the phosphorylation of AMPK, ACC, and FoxO1 ↓The G6Pase and PEPCK activities	[50]
Suppressing Gluconeogenesis	In vivo	C57BL/6 male mice were fed a high-fat diet	Geniposide (100 or 10 mg/kg) was injected intraperitoneally every day for two weeks	↓Glucose tolerance	[51]
		C57BL/6 male mice were fed a high-fat diet	Geniposide (100, 200, and 400 mg/kg) for two weeks	↓plasma glucose, body weight, TC, TG and insulin levels ↓GP and G6Pase activities and mRNA/protein expression	[52]
	In Vitro	L02 treated with 1 mmol/L insulin plus 25 mmol/L glucose for 24 h	Geniposide 1/10/100μmol/L for 24 h	↓Glucose production ↓The G6Pase and PEPCK activities ↑DEX induced FOXO1 nuclear accumulation ↑phosphorylation of AKT	[51]

Abbreviations: FoxO1, forkhead box O1; PDK4, pyruvate dehydrogenase kinase 4; PDH, Propane Dehydrogenation; GAS, gasoline; ATP, Adenosine Triphosphate; PDK1, pyruvate dehydrogenase kinase 1; Akt, AKT serine/threonine kinase; GSK3β, glycogen synthase kinase 3 beta; GLUT2, glucose transporter 2; GnT-IVa, glucosaminyl (N-acetyl) transferase family member 7; ERO1, endoplasmic reticulum oxidoreductin 1; IAPP, amyloid polypeptide; AMPK, activated protein kinase; HO-1, heme oxygenase 1; Bcl-2, B cell leukemia/lymphoma 2; BAX, BCL2 associated X, apoptosis regulator; Txnip, thioredoxin-interacting protein; PERK, Protein kinase R (PKR)-like endoplasmic reticulum kinase; eIF2α, eukaryotic translation initiation factor 2 subunit alpha; IRE1α, Inositol-requiring enzyme-1α; PDX-1, Pancreatic duodenal homeobox-1; ACaCa, acetyl-CoA carboxylase; TC, total cholesterol; TG, total triglyceride.

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medicated pancreatic islet β cell protection. Geniposide potentiates insulin secretion via activating GLP-1R and adenylyl cyclase/cAMP signaling pathways. Researchers also observed Ca^{+2} channel activation by geniposide.[39]

Apart from inhibiting the damage and apoptosis of pancreatic islet β cells, another therapeutic strategy for the protection of pancreatic β cells is to promote their regeneration. Geniposide promotes pancreatic islet β cell regeneration in vivo to balance blood glucose levels and the mechanism includes triggering duct cell differentiation by enhancing TCF7L2 expression and activating the Janus-activated kinase 2 (JAK2) / signal transducer and activator of transcription 3 (STAT3) pathway.[46]

Improving Insulin Resistance (IR)

IR is an important factor, which can lead to the onset of type 2 diabetes. IR occurs when cells in muscles, fat, and liver stop responding to insulin. Geniposide alleviates abnormal glucose tolerance and hyperinsulinemia, indicating that it has an IR-alleviating effect.[47] Geniposide promotes autophagy in HepG2 cells and significantly improves IR, which may be associated with the dynamic regulation of the P62/NF-κB/GLUT-4 pathway.[48] Zhao et al[49] pointed out that geniposide improves insulin signaling deficiency possibly through AMPK-mediated Txnip degradation in 3T3-L1 adipocytes. A regulatory mechanism study considered that geniposide could improve systemic insulin sensitivity by regulating circulating RBP4 levels.[31]

Inhibiting Hepatic Glucose Production

The liver plays a crucial role in maintaining blood glucose homeostasis by coordinating glucose storage, utilization, and production. The ability of the liver to store glycogen is typically diminished in diabetic subjects. Thus, promoting hepatic glycogen synthesis and suppression of hepatic glucose production could be more effective in the improvement of overall glycemic control. Geniposide significantly inhibits hepatic glucose production in a dose-dependent manner and the inhibitory effect is partly through AMPK activation.[50] Geniposide simultaneously stimulates glycogen synthesis in mice induced by a high-fat diet and streptozotocin injection and HepG2 cells.

Suppressing Gluconeogenesis

Hepatic gluconeogenesis is an important factor in regulating plasma glucose levels. It may be the major source of fasting blood glucose and it has been regarded as one of the main contributors to hyperglycemia in diabetes mellitus. Phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) are the key regulatory enzymes of gluconeogenesis.[50] Geniposide significantly decreases the expression of glycogen phosphorylase and G6Pase at mRNA and protein levels, as well as their activity, in a dose-dependent manner.[51] The activities of PEPCK and G6Pase were significantly suppressed by geniposide. Geniposide may reduce blood glucose levels and suppress hepatic gluconeogenesis by regulating the AKT serine/threonine kinase (AKT)-FOXO1 pathway.[52]

Effects on Lipid Metabolism

Lipid metabolism disorder is one of the main risk factors of metabolic diseases, which is characterized by abnormal content or type of triglycerides, fatty acids, or cholesterol in the serum or surrounding tissues.[53] Lipid metabolism includes three main aspects as follows: Lipolysis, lipogenesis, and lipid transportation. Regulating lipid metabolism and restoring lipid homeostasis is one of the methods for the prevention and treatment of dyslipidemia and related metabolic diseases.[54] Figure 5 summarizes the pharmacological effects of geniposide on lipid metabolism and the details are exhibited in Table 2.

Promoting Lipolysis

Fat is mostly stored in adipose and other tissues or other non-adipose tissues. Excessive accumulation of triacylglycerols (TAGs) and cholesterol esters (CEs) leads to abnormal lipid metabolism. The lipid droplets (LDs) in the cytoplasm are mainly rich in TAGs and CEs, which are considered dynamic TAG storage pools and take part in several aspects of lipid metabolism.[55]

The primary oxidative pathway for energy production in the liver is β-oxidation which takes place in the mitochondria, the predominant regulators of which are the transcription factors peroxisome proliferators-activated receptors α (PPARα) and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (Pgc1α).[56] Geniposide exerts suppressive effects on hepatic lipid accumulation in rats fed with a high-fat diet and the underlying mechanism may be related to the regulation of

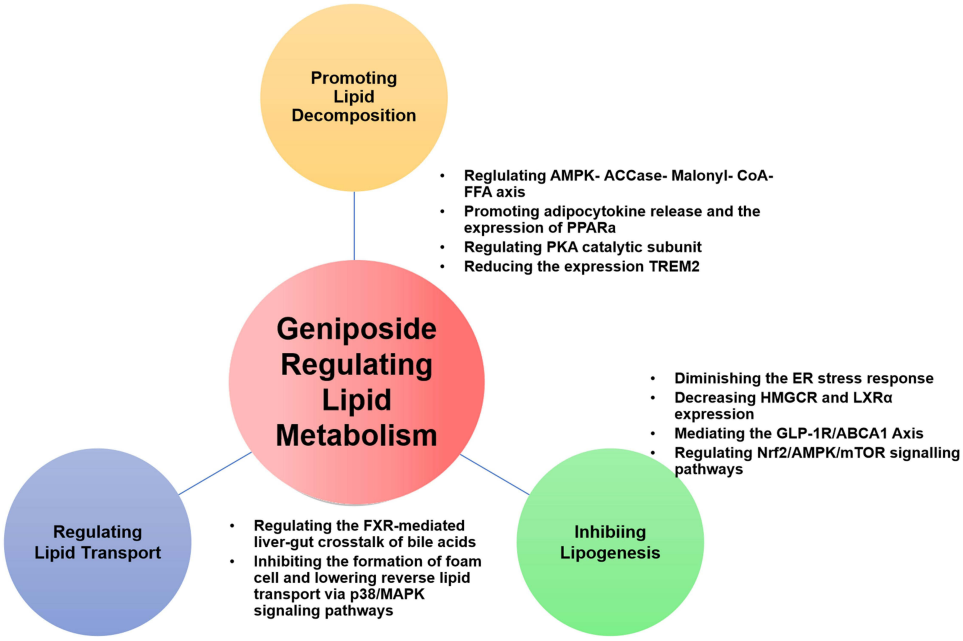

Figure 5 Pharmacological effects of geniposide on Lipid Metabolism.

adipocytokine release and PPARα expression.[57] Geniposide improves the expression of NF-E2-related factor 2 (Nrf2), PPARγ, PPARα, and heme oxygenase 1 (HO-1) and regulates the AMPK/mTORC signaling pathway in mice. Genipin, the aglycone of geniposide, inhibits intracellular lipid accumulation and significantly increases *PPARα* mRNA expression.[47] In the mitochondrion, FAs are oxidatively decomposed by carnitine palmitoyltransferase 1 (CPT1) to provide energy for other physiological processes. Sirtuin 1 (SIRT1), FoxO1, and PGC1α also control the activity of the related enzymes. Geniposide treatment alters the expression of FoxO1, PDK4, p-PDH and PDH at mRNA/protein level in the gastrocnemius of HFD-fed mice.[31] In agreement with this finding, the inhibitory effects of geniposide on the FoxO1/PDK4/PDH signaling pathway have also been reported.[30]

Lipophagy (lysosome-mediated autophagy) and cytoplasmic lipolysis are two pathways to decompose TAGs and CEs in LDs. Geniposide increases the levels of autophagy in plaque macrophages via inhibiting the triggering receptors expressed on myeloid cells 2 (TREM2)/mechanistic target of rapamycin kinase (mTOR) axis.[58] It may block the development of atherosclerosis through this mechanism. The more widely studied effect of geniposide on inflammation and oxidative stress through enhancing autophagy has been extensively studied recently, although further research is warranted.[59–63]

Activation of thermogenic adipocytes has great significance in the treatment of lipid metabolism disorders and is related to plenty of metabolic diseases. There is a new study published in 2021 different from the previous studies on the effect of geniposide on lipid metabolism. Thermogenic adipocyte is acknowledged to be a major regulator of energy homeostasis by affecting energy expenditure and glucolipid metabolism. Li et al[64] suggested that geniposide is an inhibitor of fat thermogenesis in adipocytes through regulating the PKA signaling pathway, indicating that adipocyte thermogenic capacity may be inessential for geniposide to exert its effects in obesity, and the metabolic advantage of geniposide exerted on other organs, except for adipose tissues, can indemnify for the effect of geniposide-induced thermogenic activity of adipocytes. Further research on how geniposide regulates lipolysis through influencing thermogenesis in adipocytes is warranted.

Inhibiting Lipogenesis

Excessive lipid synthesis is a major cause of lipid metabolism disorders. The *de novo* lipogenesis, FAs obtained from acetyl-CoA to fatty acyl-CoA transformation, is principally regulated by acetyl-CoA carboxylase (ACaCa) and fatty acid synthase (FASN). The central enzymatic node of saturated fatty acids (SFAs) transformed into monounsaturated fatty

Table 2 In vivo/In vitro Studies of Geniposide in Lipid Metabolism

Effect on lipid metabolism	In vivo/In vitro	Model	Dose and Duration	Experimental Outcome	References
Promoting lipidolysis	In vivo	Spontaneously obese Type 2 diabetic (TSOD) mice	0.1%/0.3% geniposide for 8 weeks	↓body weight and visceral fat accumulation ↓abnormal lipid metabolism and intrahepatic lipid accumulation ↑the mRNA levels of PPARα	[47]
		C57BL/6 male mice	Geniposide 25mg/kg for 4weeks	↓body temperature ↓the mRNA levels of genes related to thermogenesis, adipose browning, and mitochondrial function ↓ lipid deposition and UCP1 density ↓cold tolerance ↓mRNA expressions of thermogenesis-related genes: UCP1, PRDM16, CIDEA, and DIO2 in iBAT and iWAT	[64]
		Male Sprague–Dawley rats induced by a high-fat emulsion 10 mL/kg for six weeks	Geniposide 25, 50 or 100 mg/kg of was given via gavage for 6 weeks	↓the liver weights ↓serum and liver levels of TG, TC, FFA, and serum LDL-C ↑serum HDL-C ↓the liver MDA levels↑the liver SOD and GSH-Px activity ↓the fatty deposition in hepatocytes ↓the protein levels of CYP2E1 and TNFa ↑he protein levels of PPARα	[57]
	In Vitro	HepG2 cells treated with o.5mM palmitic acid for 48h	Geniposide 10/50/100μm for 48h	↓TG/TC concentration ↑the mRNA levels of PPARa	[47]
		3T3-L1 adipocyte cells treated with 1 μg/mL insulin, 500 μM IBMX, 1 μM DEX, 1 nM T3, and 5 μM rosiglitazone for 48 h	Geniposide 20 mg/mL for 24 h	↓the mRNA expressions of thermogenic genes (UCP1, PRDM16, CIDEA, DIO2, PGC1α, ELVOL3) and browning markers in adipocytes ↓ the protein levels of UCP1 and PRDM16 in adipocytes ↓ The OCRs of adipocytes ↓ the transcription activity of UCP1	[64]

Inhibitin Lipogenesis	In vivo	Male Wistar rats fed a high-fat diet for 8 weeks	Geniposide 0.001mL/g for 4 weeks	↓Weight and fat weight ↓Liver TG, FFA ↓the activity of ALT and AST ↑the protein levels of AMPK in the liver ↓the content of FAS, ACCase, and Mal-ony1-CoA in the liver	[65]
		C57BL/6J mice fed a high-fat diet for 16 weeks	Geniposide 90 mg/kg for 4 weeks	↓body weight, liver weight, HDL-C, LDL-C, serum ALT, serum AST, fasting blood glucose, and HOMA-IR ↑HDL-C	[66]
		SPF rat intramuscularly injected 5 mg/kg Dexamethasone sodium phosphat into the gluteus maximus for 14 weeks	Geniposide 50/100 mg/kg for 16 weeks	↓loss of the bone trabecula ↑the protein levels of RUNX2 and OPN in the bone trabecula of the proximal femurs ↑the protein levels of ABCA1 ↑the protein levels of GLP-1R	[69]
		Male wild-type (WT) and $Nrf2^{-/-}$ C57BL/6 mice fed Tyloxapol 500 mg/kg for 18 h	Geniposide 50/70/100 mg/kg for 19 h	↓TC, TG, LDL and VLDL ↑HDL ↓the contents of MMP-9, ApoC3, VCAM-1, ICAM-1 and MCP-1 ↓the contents of TNF-α, IL-1β and IL-6 ↑the protein levels of Nrf2 and PPARα into nucleus ↑the expression of HO-1 ↑the phosphorylation of ACC, AKT, AMPKα, AMPKβ ↓the levels of P-mTORC, P-S6K, P-S6 and SREBP-1c	[70]
	In Vitro	HepG2 cells treated with Oleate (0.1 mmol/L) and SIM (10 μmol/L) for 24 h or 28 h	Geniposide 10μmol/L for 24 or 48 h	↓the accumulation of lipid droplets ↓TC and TG content in the culture medium of HepG2 cells ↑the mRNA expression of ABCA and AMPK ↓the mRNA expression of CYP7A1, LXRα ↓the protein expression of HMGCR	[68]
		MC3T3-E1 cell incubated osteogenic induction medium for 15 days	Geniposide 10 μM or 25 μM for 15 days	↓cell differentiation ↑the protein expression of RUNX2 and OPN ↓DEX-induced cholesterol accumulation ↑the protein levels of ABCA1 and ApoA-I ↑the protein levels of GLP-1R	[69]
		HepG2 cells dealt with different concentrations of geniposide (0, 65, 130, 260, 390 and 520 μmol/L) for 24 hours with or without OA (660 μmol/L) and PA (330 μmol/L)	Geniposide 65, 130, or 260 μmol/L for 1 h	↓lipid accumulation ↑the protein levels of Nrf2, PPARα and PPARγ ↑the protein content of HO-1 in cytoplasm ↑the phosphorylation of ACC, AKT, AMPKα, AMPKβ, GSK 3β ↓the protein levels of PI3K, P-mTORC, P-S6K, P-S6, SREBP-1c and HMGB1	[72]

(*Continued*)

Table 2 (Continued).

Effect on lipid metabolism	In vivo/In vitro	Model	Dose and Duration	Experimental Outcome	References
RegulatingLipid Transport	In vivo	1. C57BL/6 male mice with high cholesterol diet ApoE$^{-/-}$ 2. mouse with nomal chow diet	Geniposide 50mg/kg/D for 13 weeks	↓serum TC/TG levels ↓hepatic TC/TG levels ↓the hepatic mRNA levels of HMGCR ↑the hepatic protein/mRNA levels of CYP7a1, CYP27a1, CYP7b1 and CYP8b1 ↓the hepatic protein/mRNA levels of FXR, MAFG, and SHP ↑the hepatic protein/mRNA levels of HNF-4α and LRH-1 ↓the protein/mRNA levels of FXR, I-BABP and ASBT in the ileum	[73]
		ApoE$^{-/-}$ mouse fed a high-fat diet for 16 weeks	50/100 mg/kg for unknown weeks	↓serum TC, TG, LDL-C, HDL-C and the development of atherosclerosis ↓the protein expressions levels of ABCA1, ABCG1 SR-A, CD36, and SR-B1 ↓p38MAPK and AKT phosphorylation	[72]
	In Vitro	HepG2 cells treated with 2.5 μm GW4064 for 12/24 h	Geniposide 100 μm for12/24 h	↓the protein/mRNA levels of FXR and MAFG ↑the protein/mRNA levels of HNF-4α and LRH-1	[73]
		Caco-2 cells treated with 2.5 μm GW4064 for 12/24 h	Geniposide 100 μm for12/24 h	↑the protein/mRNA levels of FXR and I-BABP ↓the protein/mRNA levels of ASBT	[73]
		RAW264.7 macrophage was exposed to 200mM LPA for24 h	Geniposide 50, 100 or 200 μg/mg for 24 h	↓oil red O staining and cholesterol/cholesterol ester quantitation assay ↑the mRNA and protein expression levels of ABCA1 and SR-B1 ↓the mRNA and protein levels of SR-A expression ↓p38MAPK and AKT phosphorylation	[70]

Abbreviations: PPARα, peroxisome proliferators-activated receptors α; UCP1, Uncoupling protein 1; PRDM16, PR/SET Domain 16; CIDEA, Cell Death Inducing DFFA Like Effector A; DIO2, Iodothyronine deiodinase 2; AST, aspartate aminotransferase; AMPK, activated protein kinase; TC, total cholesterol; TG, total triglyceride; Akt, AKT serine/threonine kinase; ACaCa, acetyl-CoA carboxylase; FASN, fatty acid synthase; SFAs, saturated fatty acids; SCD1, stearoyl-CoA desaturase 1; chREBP, carbohydrate-responsive element-binding protein; LDL-c, low-density lipoprotein cholesterol; VLDL, very-low-density lipoproteins; HDL, High-density lipoproteins; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, Intercellular Adhesion Molecule 1; MCP-1, Monocyte chemoattractant protein-1; CYP7A1, Cytochrome P450 Family 7 Subfamily A Member 1; LXRα, Liver X receptor alpha; PI3K, Phosphoinositide 3-kinases; mTORC, mammalian target of rapamycin complex 1; S6K, S6 kinase beta-1; P-S6, Phospho-S6; SREBP-1c, Sterol regulatory element-binding transcription factor 1; HMGB1, High mobility group box 1; SR-B1, The scavenger receptor, class B type 1; FXR, Farnesoid X receptor; MAFG, MAF BZIP Transcription Factor G; ASBT, apical sodium–bile acid transporter; MAPK, mitogen-activated protein kinase.

acids (MUFAs) is stearoyl-CoA desaturase 1 (SCD1), which is regulated by sterol regulatory element-binding transcription factor 1 (SREBP-1c), carbohydrate-responsive element-binding protein (chREBP), and LXR. Transcriptional regulation of Acc and FASN happens mainly via SREBP-1c and chREBP. Geniposide is highly effective in inhibiting lipogenesis and free fatty acid (FFA) levels in hepatic tissues were decreased significantly after geniposide treatment, whereas TG, FASN, ACaCa, and malonyl-CoA levels were significantly reduced in the geniposide group.[65] Geniposide could significantly suppress hepatic total triglyceride (TG), total cholesterol (TC), and FFA in NAFLD rodents.[66] Geniposide also decreases the expression of SREBP-1c.[67]

Cholesterol plays a central role in lipid metabolism. TC and/or low-density lipoprotein cholesterol (LDL-c) levels ultimately depend on cholesterol hypersecretion. Significantly, geniposide inhibited TC and LDL production in different animal models. High mobility group box 1 (HMGCR), squalene monooxygenase, and SREBP are all crucial players in cholesterol synthesis (the first two are rate-limiting enzymes in the biosynthetic pathway, and the latter is a master transcriptional regulator of cholesterol synthesis). Geniposide inhibited TC, TG, LDL, and very-low-density lipoprotein (VLDL) production, SREBP1-c expression, and HMGCR expression at the mRNA/protein level in vivo.[67,68] Zheng Y et al published a study focusing on cholesterol metabolism in osteoporosis in 2021, they found that geniposide can effectively ameliorate dexamethasone-induced cholesterol accumulation via activating the GLP-1R/ABCA1 axis in MC3T3-E1 cells.[69] Geniposide has significant beneficial effects on cholesterol metabolism and lipid accumulation in HepG2 cells. After HepG2 cells were treated with geniposide, the expression of *ABCA1* and *AMPK* mRNA significantly increased, while that of Cytochrome P450 Family 7 Subfamily A Member 1 (*CYP7A1)* and Liver X receptor alpha *(LXRA)* mRNA was significantly reduced.[68] Geniposide and chlorogenic acid combination can significantly reduce hepatic TG, TC, and FFA via SCD-1 suppression in the liver.[66]

Regulating Lipid Transport

Lipid transportation in the blood depends on plasma lipoproteins. High-density lipoproteins (HDL) snatch the cholesterol from other lipoproteins or the peripheral tissues and bring it back to the liver, which is called reverse cholesterol transport (RCT). In the circulation, VLDL, produced in the liver, release TGs and FFA.[71] Hepatic lipase removes TGs from intermediate-density lipoprotein, forming LDL. LDL has a high cholesterol content and it can be removed from circulation through binding to LDL receptors in extrahepatic tissues and the liver.[72]

Geniposide attenuates the development of atherosclerosis and reduces serum TC, TG, and LDL levels in ApoE-/- mice.[70] In vitro and in vivo experiments have revealed that geniposide can modify the efflux-related proteins and lipoproteins to regulate cholesterol uptake, thus balancing the lipid transport levels and eventually inhibiting the formation of foam cells. These advantages seem to be mediated by the downregulation of P-p38 mitogen-activated protein kinase (MAPK) and P-AKT.

There are two main methods of assuaging hypercholesterolemia. The first is to increase the transformation of cholesterol into bile acids in the liver and the other is enhanced RCT, through which cholesterol in the plasma can be returned to the liver for catabolism. On the one hand, geniposide improves the hepatic synthesis of bile acids via passivating the negative feedback regulation of bile acids regulated by Farnesoid X receptor (FXR).[73] On the other hand, geniposide facilitates the RCT, more cholesterol is directed from the circulation back to the liver, exerting the hypolipidemic effect of geniposide indirectly.[73] Hwa-Young Lee[74] displayed an unusual yet very clear design solution, their study was conducted using the Eucommia ulmoides Oliver extract, and its active constituents, aucubin and geniposide. They found that geniposide reduces hepatic lipid accumulation and secretion of apolipoprotein B, and they believe the mechanism may be linked to ER stress and hepatic dyslipidemia.

Discussion

Glucolipid metabolism is complex and variable, often involving multiple pathological reactions. Over the past few decades, a growing number of animal and cell model studies have revealed the potential of geniposide to ameliorate glucolipid metabolism disorders. We summarized basic information about various in vitro and in vivo studies on the pharmacological effects of geniposide on glucolipid metabolism in this review.

In terms of glucose metabolism, geniposide can increase glucose utilization and insulin production, protect pancreatic islet β-cells, inhibit IR and hepatic glucose production, and suppress gluconeogenesis. In the aspect of lipid metabolism, geniposide can promote lipid decomposition, inhibit lipogenesis, and regulate lipid transport. Geniposide regulates a wide range of factors related to glucose and lipid metabolism, including metabolic regulators AMPK, Glut2\Glut4\GLP-1R, which are indispensable in glucose metabolism, and PPARα/SREBP1c/ LXR/FXR, which regulate lipid metabolism. Such multi-pathway regulation improves the entire glycolipid metabolism network in a three-dimensional manner. However, there are still some challenges that need to be addressed.

First of all, the current research on geniposide is restricted to whole animal and cell experiments and has not included any clinical trials. Therefore, further clinical studies are essential to determine the role of geniposide in clinical therapy.

Secondly, thorough studies and precise targets are required. Studies on the effect of geniposide on glucolipid metabolism are sometimes unconvincing and have not been verified via rigorous experiments using knockout mice or cell lines. There is insufficient evidence supporting the results and conclusions of these studies. At present, research focusing on the pathological mechanisms of geniposide has not included a specific target, and future studies should be more accurate.

Furthermore, the efficacy and toxicity of geniposide need to be confirmed. We investigated several studies on geniposide toxicity that were published in 2021, and found that chronic oral toxicity in rats resulted in an impact on serum biochemical, urinary, and hematological parameters, and affected related organ weights. However, studies which reported that geniposide improves glucose and lipid metabolism have not investigated the potential toxicity of geniposide. Further studies are warranted to verify the feasibility of geniposide as a drug and develop a safe procedure for its administration. Its efficacy should also be compared with that of the current major drugs for metabolic diseases.

Conclusion

Geniposide ameliorates lipid and glucose metabolic disorders, improving the entire glycolipid metabolism network in a three-dimensional manner at the level of molecular mechanism (Figure 6). Accumulating studies, related to the effect of geniposide on glucose and lipid metabolism, have been performed. While full-scale progress has been made, the underlying mechanism of glucolipid metabolism has not yet been utterly elucidated. Future research is warranted to

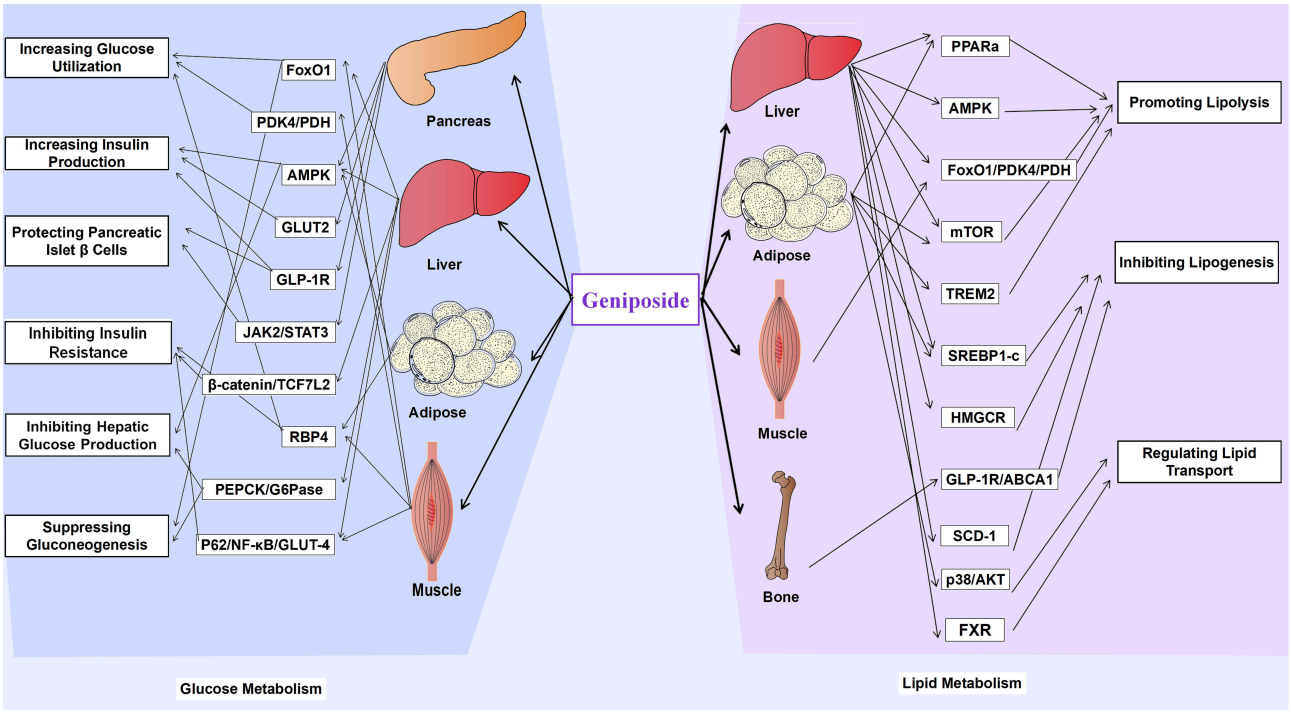

Figure 6 Molecular mechanisms involved in the regulation of glucolipid metabolism by geniposide.

explain both long- and short-term effects of geniposide on glucose and lipid metabolism. Our review affords the first systematic summary of research examining the effect of geniposide on glucolipid metabolism, which will be beneficial in the development of metabolic diseases therapy in the future and in obtaining more reproducible and reliable data.

Abbreviations

NAFLD, non-alcohol fatty liver disease; GJE, Gardenia Jasminoides Ellis; EUO, Eucommia Ulmoides Oliv; RO, Rehmannia Officinalis; RS, Radix Scrophulariae; LPO, hepatic lipid peroxidation; GST, glutathione-S-transferase; GSH, glutathione; GPx, glutathione peroxidase; CuZn-SOD, copper- and zinc-containing superoxide dismutase; ATP, adenosine triphosphate; RBP4, retinol-binding protein 4; GSIS, Glucose-stimulated insulin secretion; GLP-1R, glucagon-like peptide 1 receptors; GLUT2, glucose transporter 2; AMPK, activated protein kinase; PDI, protein disulfide isomerase; ERO1, endoplasmic reticulum oxidoreductin 1; IAPP, amyloid polypeptide; Txnip, thioredoxin-interacting protein; ER, endoplasmic reticulum; IR, Insulin Resistance; RBP4, retinol-binding protein 4; TAGs, triacylglycerols; CEs, cholesterol esters; LDs, lipid droplets; ACaCa, acetyl-CoA carboxylase; FASN, fatty acid synthase; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; SCD1, stearoyl-CoA desaturase 1; chREBP, carbohydrate-responsive element-binding protein; LDL-c, low-density lipoprotein cholesterol; VLDL, very-low-density lipoproteins; HDL, High-density lipoproteins; RCT, reverse cholesterol transport.

Disclosure

The authors report no conflicts of interest in this work.

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