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Geniposide: Enhancing β-Cell Function and Glucose Control as a Novel Antidiabetic Strategy

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Abstract Diabetes mellitus (DM) is a long-term metabolic condition associated with hyperglycemia, which either insulin resistance, insulin secretion insufficiency, or a combination of both can cause. The antidiabetic treatment options, insulin, metformin, and more recent pharmacological treatments, possess some limitations, such as adverse effects, insufficient efficacy, and poor adherence, which require safer and more thorough treatment strategies. Geniposide is a multitarget antidiabetic agent with β-cell protective and glucose homeostasis-regulatory effects. In preclinical research, geniposide inhibits hepatic gluconeogenesis by AMPK-FoxO1 signaling, raises insulin release, lowers oxidative stress and inflammation, and promotes peripheral glucose absorption through PI3K/Akt-GLUT4. Geniposide also regulates metabolic homeostasis by modulating the composition and activity of gut microbiota. It is synergistic with other bioactives, such as baicalin, berberine, crocin I, and TUDCA, which can improve its therapeutic potential and highlight the possibilities of combination therapy. Although preclinical evidence is promising, clinical trials are still limited, particularly, ideal dosing, long-term safety, and bioavailability. This review presents an overview of the mechanistic understanding, organ-specific actions, pharmacokinetic, and combination therapy prospective of geniposide with special focus on its potential as a multitarget antidiabetic biomolecule. Further studies incorporating modern drug delivery technology and clinical studies are needed to validate preclinical results into effective, safe, and patient-specific treatments against DM.

Keywords: Geniposide, Diabetes mellitus, Oxidative stress, Gut microbiota, Pancreatic β-cell protection

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Introduction Diabetes mellitus (DM), one of the most serious chronic diseases of the 21st century, currently affects over 500 million people globally and is predicted to reach 783 million by 2045 (1). Chronically raised blood sugar levels caused by either poor insulin action, ineffective insulin secretion, or both are its most significant characteristic. Type 1 diabetes mellitus (T1DM), the main autoimmune illness, is caused by the immune system attacking and killing the insulin-producing β-cells in the pancreas, leaving the patient completely insulin-deficient (2). The majority of diabetes cases worldwide are caused by T2DM, which is caused by a combination of relative insulin insufficiency and peripheral tissue insulin resistance. DM pathophysiology includes hyperglycemia, insulin resistance, and progressive β-cell dysfunction, which adds to oxidative stress, inflammation, and long-term complications. The available treatments, such as insulin, sulfonylureas, metformin, and advanced antidiabetic agents, are associated with side effects including hypoglycemia, weight gain and gastrointestinal disturbances (3). This produces the need for safer and more targets alternatives. Several antidiabetic medications, such as insulin, sulfonylureas, metformin, and drugs like GLP-1 receptor agonists and SGLT2 inhibitors, existing treatment methods have significant limitations. Pancreatic β-cells

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are essential to produce and release insulin in response to the blood glucose levels. Disruption or destruction of β-cells changes this, negatively affecting glucose uptake and use, with the resultant long-term hyperglycemia. Maintaining β-cell activity and enhancing insulin sensitivity are important interventions in achieving sustained glycemic regulation and preventing the development of long-term morbidity (4). Recent pharmacological research has shown that geniposide can prevent oxidative stress, inflammation, and apoptotic damage to pancreatic β cells, as well as increase insulin secretion, control hepatic gluconeogenesis, facilitate peripheral glucose uptake, and restore overall glucose homeostasis. The frequently observed side effects and the inconsistent long-term efficacy and adherence problems all contribute to safer and more effective treatment options.

Phytochemicals are also considered as possible therapeutic candidates due to their wide variety of pharmacological activities, reduced toxicity, and the capacity to alter several pathological pathways. The iridoid glycoside Geniposide in *Gardenia jasminoides Ellis* is traditionally used in Chinese medicine in the treatment of diabetes, jaundice, hepatitis, high blood pressure, sprains, and contusions (5). Past literature highlighted the diverse pharmacological activities of geniposide antitumor activity, anti-diabetic, antidiabetic activity, neuroprotective activity, hepatoprotective, and cholagogic activities (5,6 &7). The majority of these pharmacological actions of geniposide relate to its anti-inflammatory and antioxidant actions. The role of geniposide in the treatment of diabetes, and especially its dual action in β-cell protection and the ability to modulate glucose homeostasis, has not been completely explained. This review provides a summary of existing knowledge on the pharmacological effects and the mechanisms underlying geniposide as a multitarget antidiabetic agent, including its capacity to maintain pancreatic β-cell integrity and restore systemic glucose regulation, and its future in clinical application.

Relationship between insulin resistance and β-cell dysfunction

The basic process of glucose homeostasis

The balance between insulin secretion by pancreatic β-cells and peripheral tissue sensitivity to insulin is a highly regulated system that keeps glucose at homeostasis at normal levels (8). Glucose in the intestine is absorbed into the bloodstream after a meal (postprandial state), increasing the level of blood glucose and triggering the secretion of insulin by the pancreatic β-cells. Insulin is bound to the insulin receptor (IR), a receptor tyrosine kinase, on target cells, which undergoes autophosphorylation and insulin receptor substrates (IRS proteins, in particular, IRS-1 and IRS-2). The phosphorylated IRS proteins stimulate phosphoinositide 3-kinase (PI3K), which transforms PIP2 into PIP3 and attracts PDK1 and Akt (protein kinase B) to the membrane; PIP2 is phosphorylated by PDK1, and Akt is activated (9). Activated Akt causes various downstream effects that stimulate the uptake of glucose and inhibit the production of glucose by the hepatic cells. Activation of Akt in skeletal muscle and adipose tissue results in the phosphorylation of TBC1D4/AS160, causing translocation of GLUT4-containing vesicles to the plasma membrane and enhancing glucose uptake into cells (10). It lowers hyperglycemia by having peripheral tissues take up glucose in the blood. At the same time, Akt prevents gluconeogenesis in the liver by phosphorylating transcription factors, including FoxO1, which are excluded from the nucleus, decreasing the expression of gluconeogenic genes, including PEPCK and G6Pase. This inhibits the production of hepatic glucose. Insulin also stimulates glycogen synthesis (through inhibition of GSK3) and inhibits glycogenolysis, which also reduces glucose release by the liver. Physiological conditions, the resulting rises in liver glucose synthesis and muscle/adipose glucose uptake maintain blood glucose levels at a constant level (11). Any failure in the secretion of insulin (β-cell dysfunction) or failure in the signaling (insulin resistance) within these pathways may disrupt this balance, resulting in hyperglycemia.

The influence of insulin resistance and β-cell failure in diabetes

Insulin resistance is described as a reduced cellular response to normal levels of insulin and is one of the major abnormalities in the pathway development of T2DM (12). High concentrations of free fatty acids (FFAs), proinflammatory cytokines (TNF-α, IL-6), and oxidative stress in insulin-resistant conditions activate various serine/threonine kinases (IKKβ, JNK, mTOR/S6K), which phosphorylate insulin IRS proteins on serine residues. This phosphorylation of serine inhibits the capacity of IRS to interact with phosphatidylinositol-3-kinase (PI3K) and stops the signaling downstream, suppressing the metabolic effects of insulin (13). More phosphorylation of IRS also activates degradation or inhibits efficient tyrosine phosphorylation by the IR, enhancing the inhibition of insulin signaling. Lipid metabolites like diacylglycerol (DAG) and ceramides activate novel PKC isoforms, leading to inhibitory phosphorylation of an IR or IRS molecule and neutralize insulin effects on gluconeogenesis or glucose uptake in peripheral tissues (14). This phase is associated with pancreatic β-cells reacting to raise insulin secretion (hyperinsulinemia) to counter peripheral insulin

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resistance and keep the glucose levels close to normal. Chronic metabolic stress (such as glucotoxicity, lipotoxicity, oxidative stress, and endoplasmic reticulum stress) has toxic effects on β-cells. Over time, β-cells become functionally compromised, exhibted reduced insulin biosynthesis, impaired insulin particle exocytosis and increased apoptosis or dedifferentiation, leading to a decline in β-cell mass and secretory ability (15). The main feature of overt T2D is the inability of insulin production to deal with the pre-existing insulin resistance, and the ability of β-cells to decrease leads to persistent hyperglycemia. The transition of normoglycemia into prediabetes and ultimately to overt diabetes is caused by the peripheral tissues insulin resistance and the β-cells increasing failure.

Interaction between oxidative stress, inflammation, and β-cell dysfunction

Basic concept of oxidative stress in diabetes

Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the cells capacity to respond to this activity through antioxidant defense mechanisms (16). Chronic increases in glucose and lipid levels in the presence of diabetes increase the formation of ROS through several pathways. Pancreatic β-cells are especially susceptible to oxidative damage because they have low levels of several important antioxidant enzymes, including glutathione peroxidase (GPx), catalase, and superoxide dismutase (SOD) (17). This indicates that ROS can be efficiently obtained by the majority of other cell types. Superoxide radicals (O2-) are produced when excess intracellular glucose is oxidized by glycolysis and pumped into the mitochondrial electron transport chain. This process increases electron flux and may overload complex I and complex III, causing electrons to leak to oxygen (18). Simultaneously, higher concentrations of end-products of advanced glycation (AGEs) and their association with the AGEs receptor (RAGE) activate the NADPH oxidase enzyme, leading to excessive generation of ROS. The accumulation of ROS burden (superoxide, hydrogen peroxide, hydroxyl radicals) leads to damage of lipids (lipid peroxidation), proteins (carbonylation), and DNA, which causes cellular stress responses. ROS damage in β-cells disrupts a variety of cellular functions: it affects mitochondrial integrity (by inhibiting ATP generation required to trigger insulin release in response to stimuli), disrupts the transcription and translation of insulin genes (e.g. by destabilizing transcription factors like PDX1 and MafA), and activates stress kinases (JNK, p38 MAPK), which may induce apoptosis or dedifferentiation (19). Endoplasmic reticulum (ER) stress and the unfolded protein response (UPR), which are caused by oxidative stress, may result in damage to β-cells that are already stressed by the demands of insulin production. The β-cells cannot fight against inherited metabolic stresses as effectively as immune cells with effective antioxidant defenses because they possess the capacity to neutralize ROS and repair oxidative damage. Chronic oxidative damage is a major contributor to the pathophysiology of diabetes mellitus, causing β-cell malfunction, cell identity loss, apoptosis, or dedifferentiation over time (20).

Bidirectional communication between oxidative stress and inflammation

Pancreatic β-cells generate ROS, which have the potential to be effective stimulators of inflammatory signaling pathways and directly cause molecular damage (17). High levels of ROS stimulate transcriptional factors, including NF-kB and stress kinases, including JNK, which stimulate the production of proinflammatory cytokines. These cytokines also cause insulin signaling in both β-cells and peripheral tissues, stimulate β-cell apoptosis, and disrupt the dynamics of insulin secretion (21). These cytokines that promote inflammation contribute to the continuous cycle of oxidative stress and inflammation, which accelerates b-cell failure by increasing the production of ROS. Geniposide treatment of high glucose retinal Muller cells decreased ROS, inhibited nuclear translocation of NF-kB (p65), and decreased TNF-α, IL-1b, and IL-6 secretions, which were mediated by Nrf2 activation. The inhibition of high-glucose-induced cell adhesion in endothelial cells with geniposide was linked with low ROS generation and inhibition of NF-kB signaling. Geniposide can be utilized to reduce ROS and block NF-kB and other inflammatory signals, breaking the feed-forward loop between oxidative stress and inflammation and preventing more damage to β-cells (22). Fig. 1 shows that geniposide can integrate several signaling pathways, such as GLP-1R-cAMP/PKA, AMPK-FoxO1, PI3K/Akt, Nrf2/ HO-1, and NF-kB signaling pathways, with the effects of geniposide being increased insulin secretion, glucose uptake, and oxidative/inflammatory stress.

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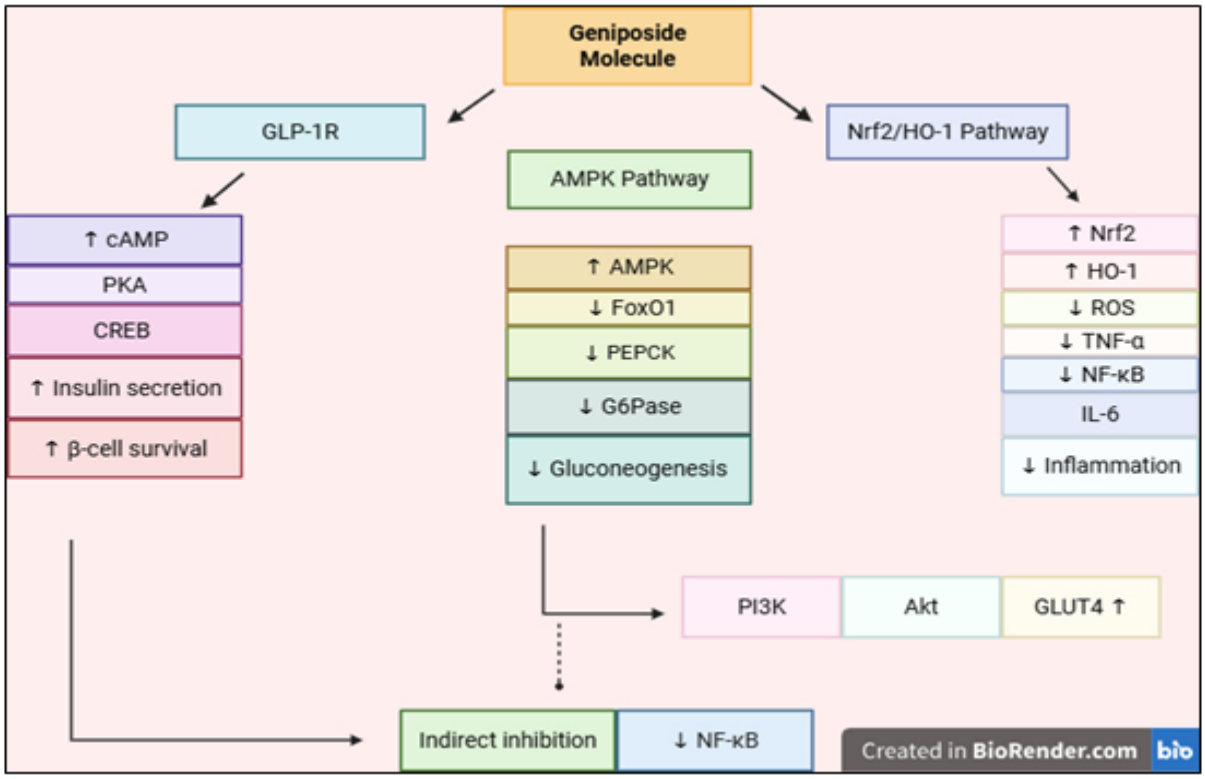

Figure 1: Molecular mechanisms of geniposide in regulating glucose homeostasis (Retrieved from Biorender)

Geniposide and organ-specific regulation of glucose homeostasis

Geniposide functions as a multitarget antidiabetic substance that affects the pancreas, liver, kidney, muscle, adipose tissue and brain (Table 1). Collectively, these factors lower blood glucose levels and improve metabolic balance by improving insulin secretion and sensitivity, suppressing gluconeogenesis, and modulating inflammatory and oxidative stress pathways (Nrf2, NF-κB, PI3K/Akt, and AMPK) as shown in Figure 2.

Liver

The liver maintains fasting blood glucose levels because it regulates gluconeogenesis and glycogen metabolism. In insulin-resistant states, enzymes like phosphoenolpyruvate carboxykinase (PEPCK), glucose-6- phosphatase (G6Pase), and glycogen phosphorylase (GP) are overexpressed, leading to overproduction of glucose in the liver (23). Geniposide is found to inhibit hepatic gluconeogenesis and glycogenolysis. Geniposide inhibited glucose production significantly in HepG2 cells in a dose-dependent manner by activating AMP-activated protein kinase (AMPK), increasing phosphorylation status of downstream targets such as acetyl-coa carboxylase (ACC) and FoxO1, and inhibiting PEPCK and G6Pase activity. The fact that AMPKa1/a2 reduction reversed the effects or that Compound C prevented the effects provided evidence of these processes. Geniposide administration (200-400 mg/kg over 2 weeks) lowered fasting glucose, serum insulin, and serum triglyceride levels in HFD-STZ induced diabetic mice but downregulated hepatic PEPCK, G6Pase, and GP (both mRNA and protein) levels and indicated a reduction in hepatic glucose production (24).

Skeletal Muscle

Skeletal muscle contributes to the majority of postprandial glucose consumption. The impaired GLUT4 translocation and the mitochondrial dysfunction frequently result in insulin resistance in muscle, causing poor glucose disposal (25). Geniposide has been reported to increase skeletal muscle glucose uptake by increasing Akt phosphorylation and facilitating GLUT4 translocation to the plasma membrane. Geniposide treatment of C2C12 myotubes enhanced Akt phosphorylation and GLUT4 membrane expression on insulin treatment, thereby leading to glucose uptake. In

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HFD-fed mice, genopside treatment improved glucose tolerance and insulin sensitivity through activation of the IRS1/PI3K/Akt pathway and restoration of mitochondrial function indicating glucose-lowering effect specifically in muscles (26).

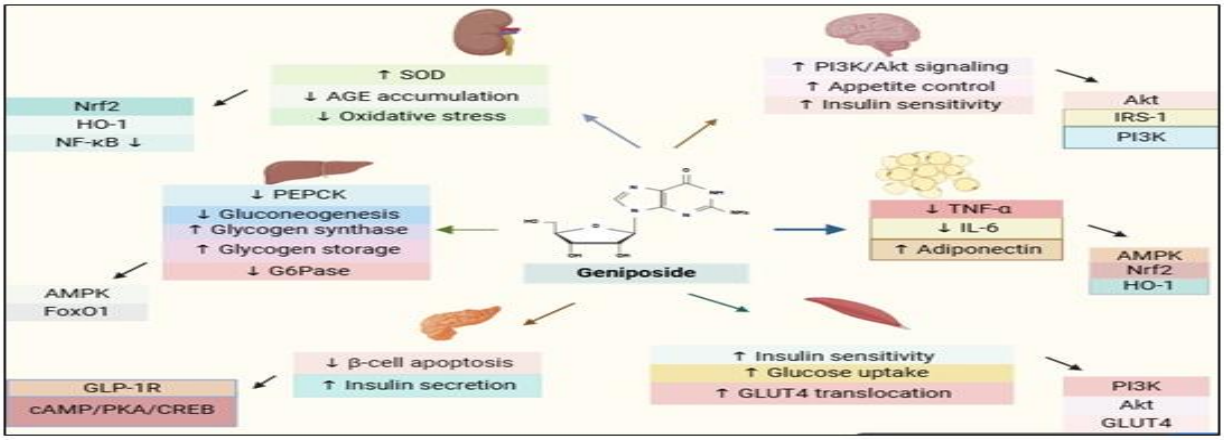

Figure 2: Organ-specific regulation of glucose homeostasis by geniposide (Retrieved from Biorender)

Adipose Tissue

Adipose tissue controls systemic insulin sensitivity through adipokine secretion, like adiponectin and leptin. Dysregulated lipolysis, increased free fatty acids (FFAs) in circulation, and low-grade inflammation are also the effects of insulin resistance that contribute to hyperglycemia and glucotoxicity (27). Geniposide alters the functions of adipose tissue by stimulating adiponectin release, decreasing pro-inflammatory cytokines (TNF-α, IL-6), and preventing excessive lipolysis. Geniposide improved the glucose uptake stimulated by insulin and the expression of adiponectin and GLUT4 in 3T3-L1 adipocytes. Geniposide treatment in HFD-induced mice improved adipose insulin sensitivity, reduced circulating free fatty acids (FFAs), reduced systemic insulin resistance, which indirectly affected the overall glucose homeostasis (28).

Table 1: Clinical and Preclinical Evidence of Geniposide in Diabetes

Compound / Regimen	Model / System	Organ / Tissue	Dose / Concentration	Treatment Duration	Mechanism / Pathway	Effect / Outcome	Reference
Geniposide (pure)	HFD+STZ diabetic mice (in vivo)	Liver	200 & 400 mg/kg, oral (daily)	2 weeks	↓GP & G6Pase (inhibits gluconeogenesis)	↓Blood glucose, ↓TG, improved hepatic enzymes.	29
Geniposide	HFD and db/db mice (in vivo)	Pancreas / islets	100 mg/kg, oral (daily)	5 weeks	Wnt/β-catenin → ↑TCF7L2, AKT activation	↑β-cell proliferation & regeneration; ↓blood glucose.	30
Geniposide (pure)	C57BL/6 DN model (HFD/STZ + UNx) (in vivo)	Kidney	50 mg/kg, oral gavage (daily)	5 weeks	AMPK → ULK1-mediated autophagy	↓Albuminuria, ↓fibrosis, improved renal function.	(31)

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Geniposide	IR HepG2 cells (in vitro)	Liver (HepG2)	62.5 µg/mL (~?) used as safe conc.; others 0.1–100 µM	4–24 h	Promotes autophagy via p62/NF-κB/GLUT4	Improved insulin sensitivity, ↑glucose uptake.	(32)
Geniposide	db/db mice	Muscle	400 mg/kg/day, oral	6 weeks	IRS1/PI3K/Akt pathway	↑Glucose uptake & insulin sensitivity	(26)
Geniposide	INS-1 pancreatic β-cells (in vitro)	Pancreatic β-cells	10–100 µM (commonly 10–50 µM)	24 h	GLP-1R activation; ↑ATP, ↑Ca^{2+} → ↑GSIS	Enhanced GSIS; protection vs high glucose.	(33)
Geniposide	Primary retinal Müller cells & C57BL/6 DR model	Retina	Cells 50 µM; mice 20–100 mg/kg (varies)	Cells 48 h; mice 2–4 weeks	Nrf2/HO-1 activation; ↓NF-κB	Reduced oxidative stress & inflammation in DR.	(34)
Geniposide	L02 hepatocytes (in vitro)	Liver cells	1 / 10 / 100 µM	24 h	↓G6Pase & PEPCK; ↑AKT phosphorylation	↓Glucose production.	(35)
Gardenia jasminoides extract (geniposide + crocin)	STZ-induced diabetic rats (in vivo)	Pancreas, liver	Extract 200 mg/kg, oral	4 weeks	AMPK activation, antioxidant	Improved glycemic control; multi-component extract.	(36)
Geniposide	HFD-fed C57BL/6 mice (in vivo)	Whole-body / metabolic	25 or 50 mg/kg, oral	8 weeks	Improve insulin sensitivity; ↓weight gain	↓FG, improved GTT/ITT.	(35)
Geniposide	INS-1E cells hIAPP toxicity (in vitro)	Pancreatic β-cells	1 / 10 / 100 µM	2 h	↑IDE, reduces hIAPP toxicity	Protected β-cells from hIAPP-induced cytotoxicity	(37)
Geniposide	Proteasome/Txnip studies INS-1 (in vitro)	β-cells	concentrations 1–100 µM	hours	Accelerates proteasome degradation of Txnip	Improved GSIS and reduced β-cell stress.	38
Geniposide	Diabetic retinopathy animal models (in vivo)	Retina	20–100 mg/kg	2–4 weeks	Nrf2 activation; ↓oxidative stress/inflammation	Attenuated retinal damage.	(34)
Geniposide	AGEs-RAGE DN model (in vivo)	Kidney	50 mg/kg or per study	weeks	Blocks AGEs-RAGE signaling	Improved DN endpoints.	(39)
Geniposide (collated studies)	Narrative/systematic reviews	Multiple organs	various (summarized)	n/a	Multiple mechanisms: GLP-1R,	Consensus: strong preclinica	(35)

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					AMPK, PI3K/Akt, autophagy, Nrf2	l evidence; clinical trials lacking.	
Geniposide 0.1% / 0.3% in diet	TSOD obese mice (in vivo)	Whole-body/metabolism	0s.1% or 0.3% in diet	8 weeks	↓Plasma glucose in OGTT	Improved glucose tolerance.	(35)
Geniposide	ApoE−/− atherosclerosis mice	Vessels / macrophages	50–100 mg/kg	8–12 weeks	Modulates macrophage polarization (M1→M2); CXCL14 pathway	Reduced plaque burden.	(39)
Geniposide topical/systemic	Diabetic wound model (STZ rats)	Skin wound	Topical conc. or systemic mg/kg (see paper)	14 days	↓TNFα, ↓IL-6; ↑VEGF	Accelerated wound healing in diabetic rats.	(40)

Role of Gut Microbiota in Geniposide-Mediated Effects

Geniposide is a bioactive compound that affects the gut microbiome, regulating metabolic pathways and providing therapeutic benefits in the management of diabetes. Geniposide supplementation is effective in causing a range of changes in the gut microbial diversity, which is associated with optimum metabolism profiles in diabetic models.

SCFAs and Metabolic Regulation

SCFAs have been reported to enhance insulin sensitivity and also to lower glucose production in the liver, which is more applicable in T2D, where the levels of SCFAs are usually low (41). Geniposide has the potential to regulate the gut-liver axis by enhancing intestinal barrier functionality and changing microbiota composition, which results in less hepatic inflammation and optimal lipid metabolism, decreasing the risk of non-alcoholic fatty liver disease. The effects of geniposide on gut microbiota can be enhanced with other bioactive compounds, including chlorogenic acid, which synergistically adjusts the composition of the microbiota and drives the farnesoid X receptor signaling pathway, and which also has increased metabolic outcomes (42). Preclinical research shows strong data on the positive effect of geniposide on gut microbiota and metabolic health. Future studies should concentrate on properly designed trials in evaluating the efficacy, safety, and long-term effects of geniposide, both as a single agent and in combination therapies, on gut microbiota and metabolic control in diabetes and related diseases.

Treatment strategy: Geniposide as a multitarget agent

Traditional monotherapies often target a single pathway, which may not offer a comprehensive approach to treating the disease. Geniposide has emerged as a promising multitarget drug that can help in the simultaneous treatment of multiple pathogenic aspects. Geniposide increases insulin sensitivity through the PI3K/Akt pathway in skeletal muscle and adipose tissue, which stimulates GLUT4 translocation and glucose uptake (43). It inhibits the process of gluconeogenesis in the liver via the AMPK-FoxO1 axis by inhibiting major gluconeogenesis enzymes (PEPCK and G6Pase) and decreasing the production of glucose in the liver. Geniposide has β-cell protective properties, reducing oxidative stress and inflammatory signaling, inhibiting apoptosis, and maintaining insulin secretion. Better glucose homeostasis and reduced hyperglycemia are the results of all these actions. Preclinical research has also identified anti-inflammatory and antioxidant effects of geniposide, including the inhibition of proinflammatory cytokines and a decrease in ROS accumulation (44). In diabetic mouse models, geniposide therapy resulted in normal lipid profiles, increased insulin sensitivity, and decreased fasting blood glucose. Its multitarget mechanisms are not limited to glucose regulation but to prevent against chronic complications, including nephropathy, neuropathy, and retinopathy through reduction of oxidative stress, AGE formation and endothelial dysfunction.

Synergistic and Combination Therapy Potential

Geniposide is also highly therapeutic because of its potential in combination therapy. The use of traditional antidiabetic drugs (e.g., metformin, berberine) or other bioactive compounds (e.g., baicalin) in combination can lead to synergistic effects, with better glycemic regulation and lipid metabolism and reduced side effects (45). These strategies take advantage of complementary actions, such

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as increased AMPK activation, antioxidant ability, and anti-inflammatory signaling, providing a complex strategy to the treatment of diabetes.

Geniposide and Baicalin

The geniposide-baicalin combination has demonstrated positive effects in regulating metabolic processes and enhancing insulin sensitivity (46). Combination therapy had a strong effect in reducing atherosclerotic plaque formation in mice on a high-fat diet, extending the proliferation of smooth muscle cells and inhibiting oxidative stress and inflammation. The mechanism behind this was connected to the suppression of Wnt1 and the strengthening of the Wnt1/DKK1 ratio, which plays an important role in vascular remodelling and the control of inflammation (47). The combination therapy prevented dendritic cell growth and infiltration into atherosclerotic lesions and the observed benefits might be partially mediated through immunomodulatory activities.

Geniposide and Berberine

Geniposide could be combined with berberine, and their combined antidiabetic effects have been studied. The glucose-lowering effects of berberine stimulate the activities of the AMPK, resulting in enhanced insulin sensitivity and lipid metabolism (48). This is enhanced when used in combination with geniposide, which also activates AMPK and has anti-inflammatory and antioxidant properties. Such a synergistic interaction may provide a more comprehensive strategy to the treatment of T2D because it can focus on multiple pathways involved in glucose and lipid metabolism.

Geniposide and Tauroursodeoxycholic Acid (TUDCA)

Geniposide and TUDCA have been explored as a combination that has the potential to protect the brain from diabetic complications. This is a strong defense against reoxygenation damage and oxygen-glucose deprivation in SH-SY5Y cells, which boosted ROS, ER stress, and controlled autophagy. Geniposide and TUDCA together prevent oxidative damage and apoptosis in neuron cells by inhibiting these cellular stress pathways, indicating that a potential solution to prevent or improve diabetes-related neurodegenerative complications (49).

Geniposide and Crocin I

Geniposide, synergistically used with crocin I, has shown a greater antidiabetic effect in a complementary manner. Preclinical research indicates that the combination has greater glucose homeostasis, insulin sensitivity, and antioxidant defense than either of the compounds alone (50). This synergistic action is associated with the regulation of major signaling pathways connected to oxidative stress and inflammation, which play a vital role in the β-cell dysfunction and metabolic disturbance in DM. The results indicate that geniposide and crocin I have the potential to be used as a multitarget agent in the treatment of T2D (51).

Geniposide and Gardenia Fruit and Eucommia Leaves

A combination of geniposide with the Gardenia fruit and Eucommia leaves has been proven to enhance various features of metabolic health. This combination in animal models significantly decreased hypertriglyceridemia and hyperglycemia by demonstrating better results in intravenous fat tolerance and intraperitoneal glucose tolerance tests. These effects are attributed to the synergistic effects the compounds have on lipid metabolism, glucose regulation, and insulin sensitivity, and indicate that this botanical combination might be used as an effective adjunctive treatment in the management of metabolic disorders (52).

Geniposide and Crocetin

Geniposide and crocetin have been shown to possess a wide range of therapeutic effects besides glucose control. Preclinical trials indicate that it reduces blood glucose and lipid levels, protects the liver and gallbladder, exhibits anti-tumor, and alleviates symptoms of depression. The combined effects of geniposide and crocetin, caused by synergistic antioxidant, anti-inflammatory, and metaprotection, highlight the potential of these drugs as a combination therapy of metabolic and systemic complications (53).

Pharmacokinetics and Bioavailability

Geniposide has differences in the pharmacokinetics with various routes of administration and pathology (49, 54). Geniposide is absorbed rapidly when administered orally, with plasma concentration achieved in 1 hour, although it is excreted quickly, within 12 hours. It has low absolute oral bioavailability (approximately 9.67%), and in rats, tissue distribution clearly demonstrates that the highest concentration of the drug is in the kidney and the lowest in the brain (55). Geniposide liposome formulations have been designed to overcome the ineffective brain targeting, with the formulations increasing half-life, brain accumulation, and therapeutic effects in models of cerebral ischemia reperfusion injury. The pharmacokinetic results of adjuvant-induced arthritis (AA) rats show the dose-dependent increases in peak plasma concentration and area under the curve (Cmax and AUC), with the high dose group exhibiting longer Tmax and half-life, indicating the reliability of its absorption and slower clearance under disease conditions (56). In a similar case, the oral delivery of geniposide in AA rats leads to an increase in plasma concentrations than in normal rats, especially at 60-360 min, which suggests that the rates of clearance change under the influence of the disease. Similar rises in AUC were found following the

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use of GJ fruit extract and pure geniposide in type 2 diabetic models, establishing that the increased systemic exposure is more likely due to geniposide itself, and not to other components of the extract. When geniposide is co-administered with baicalin in rats with middle cerebral artery occlusion (MCAO), it increases bioavailability, and when administered with berberine, it reduces bioavailability, presumably because of changes in the bioavailability of geniposide hydrolysis (57). Under MCAO condition, absorption is increased, Tmax is reduced, Cmax is elevated, and mean residence time (MRT) is prolonged compare to control rats, indicating that the pathological conditions can cause major changes in pharmacokinetics. Co-administered of genopside with other compounds Yin-Chen-Hao Tang (YCHT), Huanglianzhizi decoction and Zhi-Zi-Hou-Pu decoction (ZZPHD), enhances its absorption, AUC, and Cmax and prolonged MRT, indicating potential synergistic activity on systemic exposures (58).

Relating exposure to a genotoxic chemical to the risk of cancer

In practice, estimating chemical genotoxic potencies is exceedingly difficult, much more so than with ionizing radiation. As a result, a TD50 value- the amount that causes 50 % excess tumours after prolonged exposure – is known only for a relatively small number of toxic chemicals that are commonly used or encountered (for example in drinking water). Consequently, regulatory authorities have adopted a \default" exposure limit for chemicals that are patently genotoxic, but which cannot economically be studied exhaustively. An example for which regulations or guidelines have been issued recently recently is the case of drug impurities that are found to be genotoxic. The manufacture of many if not most synthetic chemical products such as drug substances involves highly toxic chemicals, and therefore a large number of such potential impurities must be screened for. As mentioned, the present document is concerned largely with potential genotoxic hazards that are intrinsic to drug substances. There appears to be a regulatory vacuum here, and products seem to be prescribed with less discernment than is the case with diagnostic ionising radiation (58).

Genboside interacts with metformin

Metformin is a cation at physiological pH, as it is a strong base. Hence, the absorption, distribution and excretion of Metformin depend on the transporters such as Organic Cation Transporters (OCTs), Multidrug and Toxin Extruders (MATEs) and Plasma membrane Monoamine Transporter (PMAT). The oral absorption and hepatic uptake of Metformin are mediated possibly by Organic cation transporters (OCTs) (OCT1 and OCT3) and renal excretion of Metformin is largely mediated by Metformin transporters such as Multidrug and Toxin Extruders (MATEs) MATE1 and MATE2-k and Organic cation transporter 2 (OCT2). Metformin is not metabolized and excreted unchanged in urine10 and the patients with moderate and severe chronic renal impairment (CRI) should not be administered with metformin. As Metformin is not metabolized, it is not expected to be involved in many drug–drug interactions (DDIs) (58).

Future Prospective

Geniposide has great potential as a multitarget antidiabetic agent, and future research will extend the therapeutic potential of this agent with the current preclinical results. Further technologies in formulation, e.g., nanoparticles, liposomes, and co-delivery systems, can enhance its bioavailability, tissue-specific targeting, increase its efficacy, and decrease possible side effects (59). It is possible to investigate the use of combination therapies with other natural compounds or conventional antidiabetic medications, which may possess a synergistic effect and may provide more comprehensive benefits in controlling T2D and its complications. If geniposide is incorporated into personalised medicine strategies, informed by patient-specific metabolism or gut microbiome composition, then therapeutic outcomes can be enhanced (60). Geniposide is expected to become a clinically viable treatment for diabetes, metabolism, and overall health if properly carried out clinical trials assist in explaining its safety, dosage, and long-term effects.

Conclusion

Geniposide is a promising multitarget therapeutic agent against diabetes mellitus because it protects pancreatic β-cells, suppresses oxidative stress and inflammation, inhibits hepatic gluconeogenesis, stimulates peripheral glucose uptake, and has a beneficial effect on gut microbiota. Its two-fold capability as a monoherapy and synergistic agent to other bioactives highlights its integrative potential in glycemic management and prevention of diabetes-related complications. However, it will require extensive research to determine the optimal dosage, long-term safety, bioavailability, and patient-specific efficacy before it's used in clinical practice. Geniposide may become a safe and effective alternative to treating diabetes and metabolic health with the development of formulation and targeted medicine.

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Conflict of Interest

No conflict of interest is declared by the authors

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