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RECEIVED 25 December 2024

ACCEPTED 19 March 2025

PUBLISHED 07 April 2025

CITATION

Ou X, Yu Z, Pan C, Zheng X, Li D, Qiao Z and
Zheng X (2025) Paeoniflorin: a review of its
pharmacology, pharmacokinetics and toxicity
in diabetes.

Front. Pharmacol. 16:1551368.

doi: 10.3389/fphar.2025.1551368

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Paeoniflorin: a review of its pharmacology, pharmacokinetics and toxicity in diabetes

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The escalating global prevalence of diabetes underscores the urgency of addressing its treatment and associated complications. Paeoniflorin, a monoterpenoid glycoside compound, has garnered substantial attention in recent years owing to its potential therapeutic efficacy in diabetes management. Thus, this study aims to systematically overview the pharmacological effects, pharmacokinetics and toxicity of paeoniflorin in diabetes. Plenty of evidences have verified that paeoniflorin improves diabetes and its complication through reducing blood sugar, enhancing insulin sensitivity, regulating gut microbiota and autophagy, restoration of mitochondrial function, regulation of lipid metabolism, anti-inflammation, anti-oxidative stress, inhibition of apoptosis, immune regulation and so on. Paeoniflorin possess the characteristics of rapid absorption, wide distribution, rapid metabolism and renal excretion. Meanwhile, toxicity studies have suggested that paeoniflorin has low acute toxicity, minimal subacute and chronic toxicity, and no genotoxic or mutational toxic effects. In conclusion, this paper systematically elucidates the potential therapeutic application and safety profile of paeoniflorin in diabetes management.

KEYWORDS

paeoniflorin, diabetes, pathogenesis, pharmacology, pharmacokinetics, toxicity

1 Introduction

Diabetes is an escalating chronic metabolic disorder globally, primarily characterized by elevated blood glucose levels resulting from inadequate insulin secretion or impaired insulin function (Tokarz et al., 2018; Sims et al., 2021). Persistent hyperglycemia not only precipitates various microvascular complications, such as diabetic nephropathy (DN) and retinopathy, but also elevates the risk of macrovascular complications, including cardiovascular diseases and neuropathy, significantly compromising patients' quality of life and lifespan (Malik, 2020; Jansson Sigfrids et al., 2021; Hermans et al., 2022; Li X. et al., 2023). Thus, currently diabetes is frequently accompanied by the diabetic nephropathy, diabetic peripheral neuropathy, diabetic wound, diabetic liver injury, diabetic myocardial ischemic injury, diabetic retinopathy and so on. In recent decades, considerable advancements have been achieved in diabetes and its complications' treatment. However, oral antidiabetic medications and insulin therapy despite effectively control blood glucose, but frequently bring about multiple side effects. Meanwhile, unstable therapeutic outcomes and necessitate long-term usage constrain clinical application seriously (Levy et al., 2019; McAlister et al., 2021; Gorgogietas et al., 2023).

Recently, natural products have increasingly been spotlighted as potential novel strategies for diabetes and its complications' treatment (Yang X. et al., 2022; Wang et al., 2023a). Notably, Paeoniflorin (PF), a principal bioactive compound in traditional Chinese herbs (*Paeonia lactiflora* Pall.), has garnered significant attention due to its remarkable hypoglycemic properties, protective effects on pancreatic β -cells, and amelioration of diabetic complications (Luo W. et al., 2023; Liang et al., 2024; Wu et al., 2024). Study indicated that hypoglycemic effects of PF *via* enhancing insulin sensitivity, stimulating insulin secretion, inhibiting hepatic glycogenolysis, and augmenting muscle glucose uptake (Gu et al., 2016; Yao et al., 2021; Zhang et al., 2023a; Zhang et al., 2023b). Furthermore, PF could improve pancreatic β -cells *via* antioxidative, anti-inflammatory, and antifibrotic pathways, mitigating the incidence and progression of diabetic complications (Zhang et al., 2020; Liu et al., 2023a). As research into the mechanism of action of PF intensifies, an increasing number of clinical and experimental studies have validated its potential therapeutic value in managing diabetes and its complications. Multiple studies have demonstrated that PF can markedly lower blood glucose levels, enhance pancreatic function, and attenuate the onset and progression of diabetic nephropathy, while also displaying favorable safety and tolerability profiles (Bayan et al., 2022).

Nonetheless, numerous questions persist concerning PF's mechanism of action in diabetes and its complications' treatment, including its specific targets, action pathways, and potential interactions with other antidiabetic medications, necessitating further exploration. Therefore, this article aims to comprehensively summarize and analyze the research progress on PF's role in treating diabetes and its complications, furnishing a scientific foundation for its expanded clinical application and introducing novel insights and approaches to refine and innovate diabetes and its complications' therapeutic strategies (Figure 1). All abbreviations along with their full forms as shown in (Table 1).

2 Pathogenesis

2.1 Insulin dysfunction

Diabetes is a chronic metabolic disorder marked by high blood glucose levels resulting from inadequate insulin secretion or resistance to insulin action. Pancreatic dysfunction, particularly the impairment of β -cells responsible for insulin secretion, is a pivotal factor in the development of diabetes (MacDonald and Rorsman, 2023; Krause and De Vito, 2023). The islets of Langerhans, alternatively termed pancreatic islets, are microorgans dispersed throughout the pancreas, playing a vital role in maintaining glucose homeostasis (Bader et al., 2016). Under normal physiological conditions, β -cells within the islets secrete insulin in response to elevated blood glucose levels, facilitating glucose uptake and utilization by peripheral tissues, including muscle and adipose tissue, while suppressing hepatic glucose production (Bennet et al., 2016; Ling et al., 2016). However, in diabetic patients, impaired function and a decreased number of pancreatic β -cells result in inadequate insulin secretion or insulin resistance.

TABLE 1 List of abbreviations and the corresponding full terms.

Abbreviation	Full terms
3-NT	3-nitrotyrosine
AGEs	Advanced glycation end products
ACC	Acetyl-coa Carboxylase
AGEs	Advanced glycation end products
Akt	Protein kinase B
ALT	Alanine aminotransferase
AMC	Anti-diabetic monomer combination
ARE	Antioxidant response element
Arg-1	Arginase-1
ASC	Apoptosis-associated Speck-like protein containing a caspase recruitment domain
α -SMA	Alpha-Smooth Muscle Actin
AST	Aspartate aminotransferase
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
BRB	Blood-retinal barrier
CaMK	Calcium/calmodulin-dependent protein kinase
Caspase	Cysteine-dependent Aspartate-specific Protease
CAT	Catalase
CD31	Cluster of Differentiation 31
CD86	Cluster of Differentiation 86
CGRP	Calcitonin gene-related peptide
CHOP	CCAAT/enhancer-binding protein Homologous Protein
Col-I	Collagen type i
Col-VI	Collagen type vi
CREB	Camp Response Element-Binding Protein
CRISPR-Cas9	Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein 9
CXCR2	C-x-c motif chemokine receptor 2
CYP2E1	Cytochrome p450 family 2 subfamily e member 1
DFU	Diabetic foot ulcers
DLI	Diabetic liver injury
DN	Diabetic nephropathy
DPN	Diabetic peripheral neuropathy
DR	Diabetic retinopathy
DRG	Dorsal root ganglion
EAF	Ethyl acetate extract
EMT	Epithelial-mesenchymal transition
ER	Endoplasmic reticulum

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TABLE 1 (Continued) List of abbreviations and the corresponding full terms.

Abbreviation	Full terms
FBG	Fasting blood glucose
FFA	Free fatty acids
GADA	Glutamic acid decarboxylase antibodies
GDM	Gestational diabetes mellitus
GFAP	Glial fibrillary acidic protein
GIP	Glucose-dependent insulintropic peptide
GLAST	L-glutamate/L-aspartate transporter
GLP-1	Glucagon-like peptide-1
GPX4	Glutathione peroxidase 4
GRP78	Glucose-regulated protein 78
GRP78/Bip	Glucose-regulated protein 78/binding immunoglobulin protein
GS	Glutamine synthase
GSH-PX	Glutathione peroxidase
GSK3β	Glycogen synthase kinase 3 beta
HDL-C	High-density lipoprotein cholesterol
HFD	High-fat diet
HOMA	Homeostasis model assessment
HUVECs	Human umbilical vein endothelial cells
IAA	Insulin antibodies
IBA-1	Ionized calcium binding adaptor molecule 1
ICA	Islet cell antibodies
ICAM-1	Intercellular adhesion molecule 1
ICV	Intracerebroventricular
IKK	IκB kinase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IRE1α	Inositol-Requiring Enzyme 1 alpha
IRS-1	Insulin receptor substrate-1
IκB	Inhibitor of κB
JAK	Janus kinase
LD50	Lethal dose
LDL-C	Low-density lipoprotein cholesterol
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1 (ccl2)
MDA	Malondialdehyde
MMP-9	Matrix metalloproteinase 9
mTOR	Mechanistic target of rapamycin

(Continued in next column)

TABLE 1 (Continued) List of abbreviations and the corresponding full terms.

Abbreviation	Full terms
MyD88	Myeloid differentiation primary response 88
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor kappa B
NLRP3	NOD-like receptor family pyrin domain containing 3
Nrf2	Nuclear factor erythroid 2-related factor 2
p-4E-BP1	Phosphorylated eukaryotic translation initiation factor 4e-binding protein 1
PEPCK	Phosphoenolpyruvate carboxykinase
PF	Paeoniflorin
PFK	Phosphofructokinase
PI3K	Phosphatidylinositol 3-kinase
PIM2	Proviral Integration site for Moloney murine leukemia virus 2
PIPK	Phosphatidylinositol phosphate kinase
p-IRF3	Phosphorylated Interferon Regulatory Factor 3
PKCβ1	Protein kinase C beta 1
Pmpca	Peptidase mitochondrial processing alpha
PPAR	Peroxisome proliferator-activated receptor
Prx3	Peroxiredoxin 3
p-SGK1	Phosphorylated Serum/Glucocorticoid Regulated Kinase 1
RAGE	Receptor for advanced glycation end-products
ROS	Reactive oxygen species
RPA	Radix paeoniae alba
SIRT1	Sirtuin 1
Smad	Mothers against decapentaplegic homolog
SOCS	Suppressor of cytokine signaling
SOD	Superoxide dismutase
SREBP1	Sterol regulatory element-binding protein 1
SSYX	Shensong yangxin capsule
STAT	Signal transducer and activator of transcription
STZ	Streptozotocin
Sumo	Small Ubiquitin-like Modifier
SYT	Sanye tablet
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAOC	Total antioxidant capacity
TC	Total cholesterol
TG	Triglycerides
TGF-β1	Transforming growth factor-β1

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TABLE 1 (Continued) List of abbreviations and the corresponding full terms.

Abbreviation	Full terms
TLR2/4	Toll-like receptor 2/4
TNF- α	Tumor necrosis factor- α
TRIF	TIR-domain-containing adapter-inducing interferon- β
TRPV1	Transient receptor potential vanilloid 1
Trx2	Thioredoxin
TrxR2	Thioredoxin reductase 2
TXNIP	Thioredoxin-interacting protein
VEGF2	Vascular endothelial growth factor receptor 2
XBP-1	X-box Binding Protein 1
α 2-AR	Alpha-2 adrenergic receptor
γ GCS	Gamma-Glutamylcysteine Synthetase

2.1.1 Insufficient insulin secretion

Insulin, secreted by the β -cells in the pancreas, plays a vital role in regulating blood glucose levels. Its main function is to facilitate glucose uptake and utilization by muscle and fat cells, thereby lowering blood glucose levels. Diminished function or quantity of β -cells results in reduced insulin secretion, causing persistent elevation of blood glucose levels (Kalogeropoulou et al., 2008).

In Type 1 diabetes (T1D), inadequate insulin secretion results primarily from autoimmune-mediated damage and death of insulin-secreting cells (Beck et al., 2019). This chronic autoimmune disease occurs when the immune system misidentifies β -cells as foreign and generates antibodies and cytotoxic T cells that attack and destroy these cells. Over time, a gradual decline in the number of β -cells in the pancreas leads to inadequate insulin secretion and ultimately hyperglycemia (Skyler, 2023). Differently, Type 2 diabetes (T2D) primarily results from chronic insulin resistance (Santoro and Kahn, 2023). As the body's insulin demand rises, the pancreas augments insulin secretion to meet the increased need. However, insulin resistance reduces cellular responsiveness to insulin, necessitating increased insulin levels to maintain normal blood glucose levels. Over time, a progressive decline in pancreatic β -cell function may result in inadequate insulin secretion.

2.1.2 Insulin resistance

Insulin resistance is a primary pathogenic mechanism in T2D and a significant factor contributing to inadequate insulin secretion. It denotes a diminished responsiveness of cells to insulin, leading to impaired insulin biological activity (Gerich, 2003). To maintain normal blood glucose levels, increased insulin secretion is required. Primary causes of insulin resistance encompass obesity, unhealthy dietary habits, and physical inactivity. Obesity, particularly abdominal obesity, constitutes a predominant risk factor for insulin resistance. Fat cells serve not only as energy reservoirs but also as sources of various hormones, including tumor necrosis factor- α (TNF- α) and leptin. These hormones can suppress insulin signaling, contributing to insulin resistance (Kirwan et al., 2002).

With worsening insulin resistance, the pancreas must increase insulin secretion to sustain normal blood glucose levels. Prolonged overwork can result in a progressive decline in the function of pancreatic β -cells, ultimately causing inadequate insulin secretion. Additionally, insulin resistance can result in aberrant hepatic glycogen metabolism (Lei et al., 2019). Insulin's primary function is to inhibit hepatic glycogenolysis and gluconeogenesis. In the presence of insulin resistance, this inhibitory effect diminishes, resulting in heightened hepatic glycogenolysis and elevated glucose release into the bloodstream.

2.2 Hepatic glycogen metabolic disorders

The liver is essential for maintaining blood glucose homeostasis through the storage and release of glycogen to regulate blood sugar levels (Zhang et al., 2022a). Insulin's primary function is to inhibit hepatic glycogenolysis and gluconeogenesis. However, in cases of insulin resistance or inadequate insulin secretion, this inhibitory effect diminishes, resulting in increased glycogenolysis in the liver and elevated glucose release into the bloodstream, leading to higher blood sugar levels.

Insulin inhibits the activity of hepatic glycogen enzymes, including glycogen phosphorylase and glycogen synthase, reducing glycogen breakdown and lowering glucose release into the bloodstream. Moreover, insulin facilitates the conversion of liver glucose into glycogen for storage, reducing blood glucose levels (Villagarcía et al., 2018). Furthermore, insulin suppresses the activity of pivotal enzymes in hepatic gluconeogenesis, including phosphofructokinase and phosphoenolpyruvate carboxykinase (PEPCK), decreasing glucose production from non-carbohydrate sources (Zheng et al., 2016). However, insulin resistance and insufficient insulin secretion lead to reduced insulin inhibition of glycogen enzymes, decreased insulin promotion of glycogen synthesis, increased glucose production from non-carbohydrate substrates, enhanced glycogen breakdown, diminished glycogen storage in the liver, and elevated glucose release into the bloodstream, exacerbating elevated blood sugar levels.

Abnormal hepatic glycogen metabolism significantly contributes to the onset of diabetes and inadequate blood glucose control (Reed et al., 2021). Hyperglycemia exacerbates the damage to pancreatic β -cells, intensifying insulin deficiency and insulin resistance, establishing a vicious cycle. Furthermore, chronic hyperglycemia can result in multiple microvascular complications, including diabetic nephropathy and diabetic retinopathy.

2.3 Abnormal intestinal hormones

Intestinal hormones, including glucagon, insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulintropic polypeptide (GIP), play a critical role in regulating blood glucose and energy metabolism. These hormones work in concert to influence key physiological processes such as appetite control, gastrointestinal motility, insulin secretion, and insulin resistance, ensuring glucose homeostasis (Sandoval and D'Alessio, 2015; Bany et al., 2023). Among them, GLP-1, secreted by intestinal L cells, is particularly important for stimulating insulin release, suppressing glucagon secretion, slowing gastric emptying, and reducing appetite,

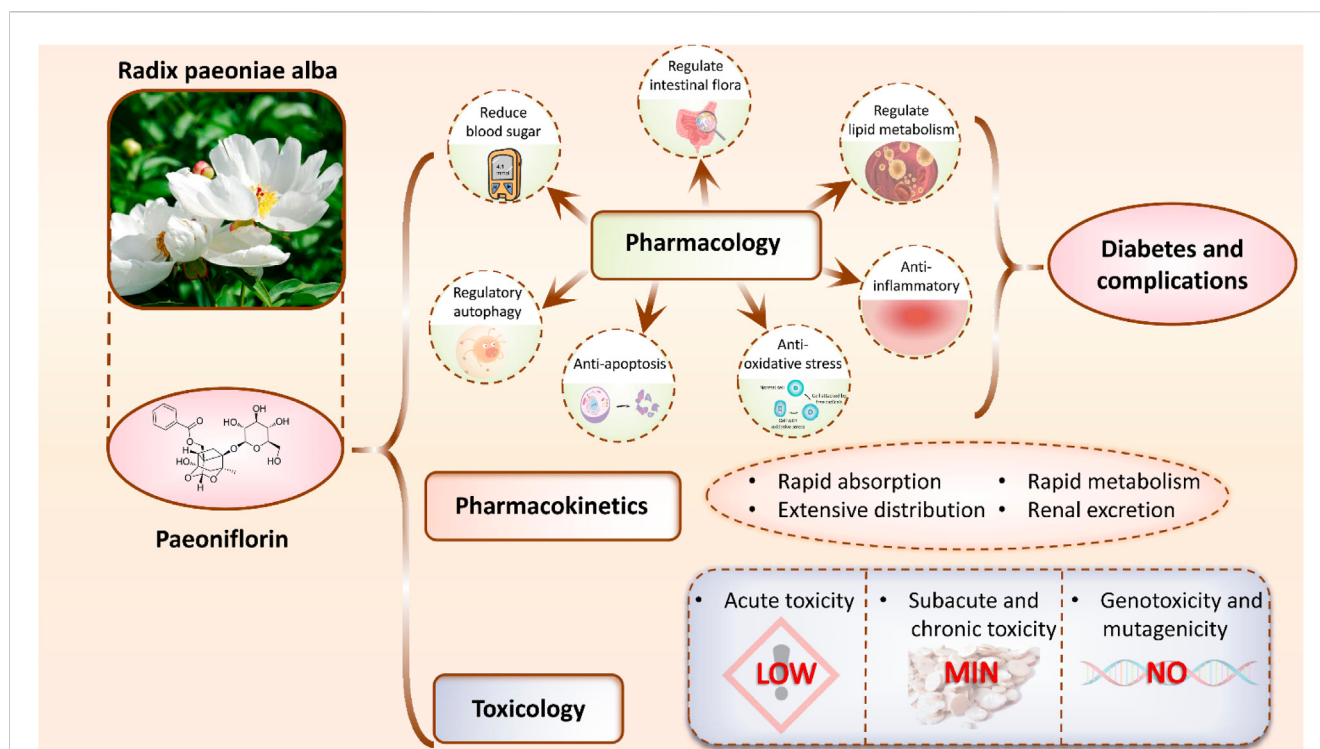


FIGURE 1
Mechanisms of PF in the treatment of diabetes and its complications. PF exerts therapeutic effects by lowering blood glucose levels, modulating gut microbiota, regulating lipid metabolism, and exhibiting anti-inflammatory, antioxidant, anti-apoptotic, and autophagy-regulating properties. In addition, its pharmacokinetics and toxicological profiles are summarized, highlighting the compound's potential as a therapeutic agent for diabetes and its associated complications.

all of which contribute to lowering blood glucose levels. Additionally, GLP-1 supports pancreatic β -cell function by promoting cell proliferation, differentiation, and survival, thereby preserving insulin production capacity (Caruso et al., 2023). However, in type 2 diabetes, both GLP-1 secretion and activity are impaired, leading to insufficient insulin release and excessive glucagon levels, which exacerbate glucose dysregulation (Bossart et al., 2022).

GIP, another key intestinal hormone, also stimulates insulin secretion and enhances β -cell function. Unlike GLP-1, GIP levels in diabetic patients may remain normal or even increase; however, its ability to enhance insulin secretion is significantly diminished due to reduced β -cell responsiveness. As a result, GIP fails to effectively regulate blood glucose, further contributing to metabolic dysfunction. Beyond their role in glucose metabolism, intestinal hormones also influence appetite and gastrointestinal function. For instance, reduced GLP-1 levels accelerate gastric emptying, causing more rapid postprandial glucose spikes and worsening insulin resistance (Hædersdal et al., 2022).

Intestinal hormone imbalances extend beyond glucose regulation, playing a crucial role in lipid metabolism and inflammation. GLP-1 and GIP not only modulate blood glucose but also influence body weight and energy balance by regulating lipid metabolism pathways (Pathak et al., 2018). GLP-1 enhances fat oxidation, decreases hepatic fat synthesis, and improves lipid homeostasis. However, in individuals with obesity and diabetes, impaired GLP-1 secretion or function contributes to increased appetite, fat accumulation, and disrupted

energy metabolism, further exacerbating obesity and insulin resistance (Guardado Mendoza et al., 2015; Derbenev and Zsombok, 2016). Chronic hyperglycemia, insulin resistance, and lipid abnormalities can also induce a persistent inflammatory state, triggering excessive release of pro-inflammatory cytokines such as TNF- α and IL-6. These inflammatory mediators not only impair β -cell function but also suppress GLP-1 secretion from intestinal L cells, further disrupting hormonal balance (Wong et al., 2022). Additionally, inflammation interferes with intestinal hormone receptor signaling, diminishing the effects of GLP-1 and GIP on β -cell function and further impairing glucose homeostasis (Li et al., 2021a).

Addressing intestinal hormone imbalances is essential for improving metabolic health in diabetes. Therapeutic strategies targeting GLP-1 and GIP pathways, such as GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, have shown promise in restoring glucose regulation and improving metabolic outcomes (Natale et al., 2025). Understanding the interplay between intestinal hormones, lipid metabolism, and inflammation may provide new avenues for the management of diabetes and its associated complications.

2.4 Obesity and abnormal lipid metabolism

Obesity is intrinsically connected to abnormal lipid metabolism, with both factors exerting mutual influence and contributing jointly to the pathogenesis of diabetes (Hu et al., 2022). Obesity induces the

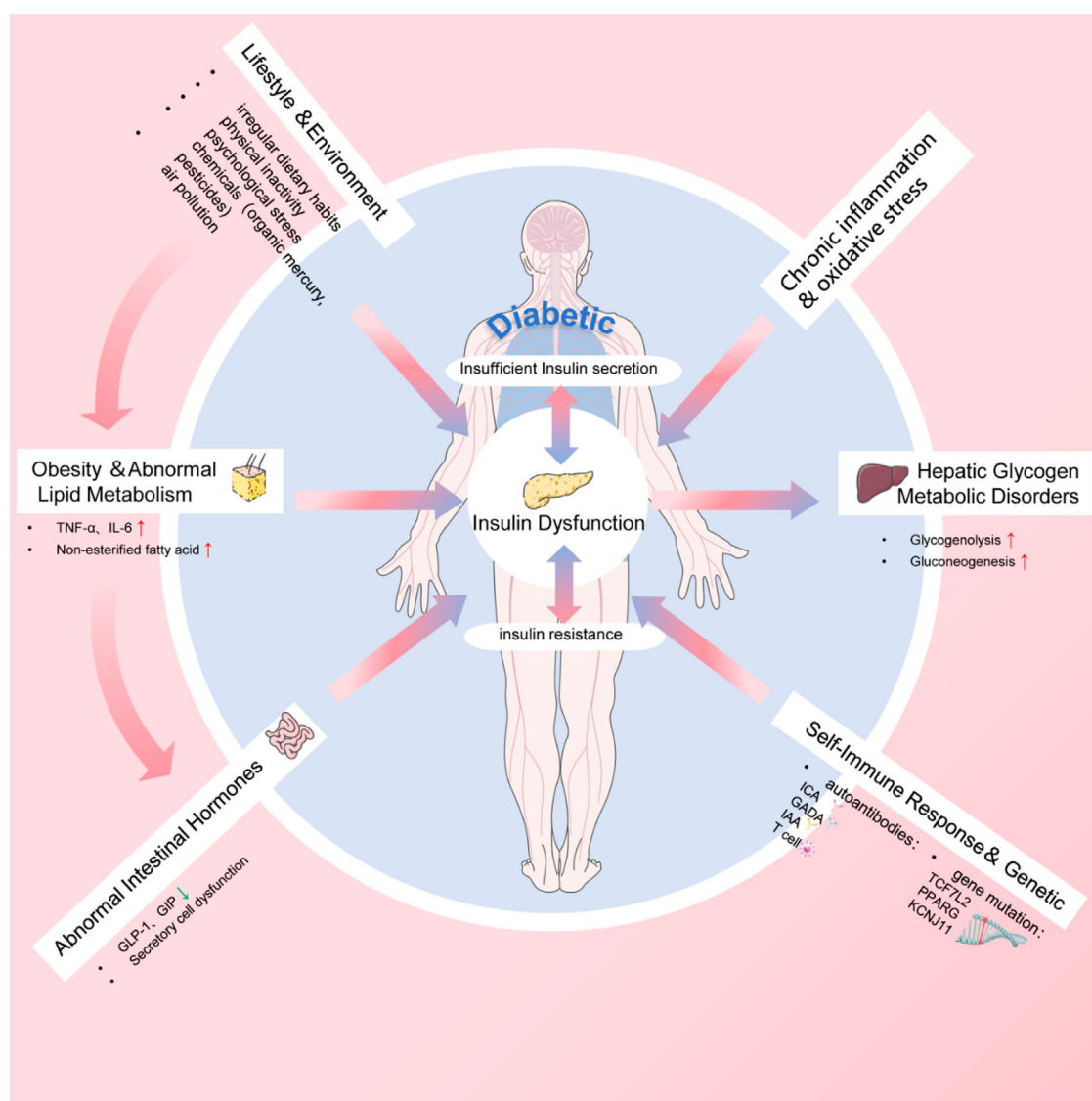


FIGURE 2
The pathogenesis of diabetes.

excessive expansion and dysfunction of adipose tissue, disrupting the normal regulation of lipid metabolism. Adipose tissue serves not only as an energy storage site but also as an endocrine organ capable of secreting various bioactive substances, including leptin, TNF- α , and interleukin-6 (IL-6) (Oikonomou and Antoniadou, 2019). Specifically, leptin functions as a hormone that promotes satiety and energy expenditure; reduced leptin secretion can result in increased appetite and excessive energy intake. On the other hand, TNF- α and IL-6 act as pro-inflammatory factors that increase insulin resistance. Their excessive secretion can impair the body's insulin signaling pathway, thereby exacerbating insulin resistance and elevating blood glucose levels.

Secondly, obesity leads to abnormal lipid metabolism, manifesting as dyslipidemia and increased lipid accumulation in adipose tissue. Individuals with obesity frequently exhibit dyslipidemia, characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), reduced high-density lipoprotein

cholesterol (HDL-C), and increased triglycerides (TG). These lipid abnormalities are risk factors for cardiovascular disease and can further aggravate insulin resistance and the progression of diabetes (Fu et al., 2011). Within adipose tissue, the overaccumulation of lipids triggers inflammatory responses in adipocytes and interferes with the insulin signaling pathway, exacerbating insulin resistance (Song et al., 2023).

2.5 Chronic inflammation and oxidative stress

Chronic inflammation and oxidative stress are critical contributors to impaired islet function and insulin sensitivity in diabetes. Low-grade, persistent inflammation is a hallmark of type 2 diabetes, particularly in obese individuals, where infiltrating macrophages in adipose tissue secrete pro-inflammatory

TABLE 2 Mechanism of PF in diabetes and complications.

Disease	Model Methods	Animal/Cell lines	Dose/Concentration	Efficacy	Mechanisms	Ref
Diabetes	—	NOD mice	100 mg/kg(i.g.)	Regulate gut microbiota	Anti-Inflammatory, Immunoregulation, ZO-1↑, ZO-2↑, OCCLUDIN↑, IL-6↓, IL-1β↓, Th1/Th17↓, MyD88/TRIF↓	Luo W. et al. (2023)
	STZ 60 mg/kg	Wistar rats	1 mg/kg(i.v.)	Reduce blood sugar	—	Hsu et al. (1997)
	HFD, 12 weeks	C57BL/6J	6.19 mg/kg(i.g.)	Regulate bacteria-cometabolism-inflammation responses	Anti-Inflammatory, Suppress insulin resistance, InsR↑, IRS-2↑, p-Akt↑, TNF-α↓, IL-1β↓, IL-6↓	Han et al. (2020)
DN	STZ 50 mg/kg, 5 days	C57BL/6J	100 mg/kg(i.g.)	Alleviate macrophage infiltration	Anti-Inflammatory, iNOS↓, TNF-α↓, IL-1β↓, MCP-1↓, JAK2/STAT↓	Zhu et al. (2017)
	AGEs 200 μg/mL, 24h	HBZY-1	50 μM	Inhibit Mesangial cell autophagy	Reduce the number of autophagosomes, LC3II/LC3I↓, RAGE↓, Col-IV↓, p-mTOR↑	Chen et al. (2017)
	STZ 65 mg/kg(iv)	SD rats	10 mg/kg(p.o.)	—	Anti-Inflammatory, TGF-β↓, Col-IV↓, ICAM-1↓	Fu et al. (2009)
	STZ 50 mg/kg, 5 days	C57BL/6J	100 mg/kg(i.g.)	Alleviate macrophage infiltration	Anti-Inflammatory, TNF-α↓, IL-1β↓, MCP-1↓, iNOS↓, CD68↓, TLR4↓, NF-κB p65↓, MyD88↓, p-IRAK1↓, Trif↓, p-IRF3↓	Shao et al. (2019)
	STZ 50 mg/kg, 5 days	C57BL/6J, TLR2 ^{-/-} mice	100 mg/kg(i.p.)	Alleviate macrophage infiltration	Anti-Inflammatory, NF-κB p65↓, TNF-α↓, IL-1β↓, MCP-1↓, MyD88↓, p-IRAK1↓	Shao et al. (2017)
	—	db/m, db/db mice	60 mg/kg(i.p.)	Inhibit macrophage activation	Anti-Inflammatory, iNOS↓, TNF-α↓, IL-1β↓, MCP-1↓, TLR2↓, TLR4↓, MyD88↓, p-IRAK1↓, Trif↓, p-IRF3↓, NF-κB p65↓	Zhang et al. (2017)
DN	Glucose 40 mM, 48 h; STZ 50 mg/kg, 5 days	MPC5; C57BL/6J	40 μM; 200 mg/kg(i.p.)	Inhibit apoptosis	Anti-Inflammatory, TNF-α↓, IL-1β↓, WT-1↑, SYNPO↑, p-MLKL↓, RIPK1/RIPK3↓	Wang et al. (2022b)
	Glucose 1 g/L	HBZY-1	10 ⁻⁶ - 10 ⁻³ M	—	Anti-oxidative stress, Anti-Inflammatory, IL-6↓, MCP-1↓	Zhang et al. (2013)
	Glucose 30 mM, 48 h	Mouse mesangial cells	200 μM	—	Anti-oxidative stress, NADPH↓, ROS↓, TGF-β↓, fibronectin↓	Sun et al. (2015)
	Glucose 30 mM, 48 h	BMDMs	10 ⁻⁸ - 10 ⁻⁴ M	—	Anti-Inflammatory, TLR2↓, iNOS↓, MyD88↓, p-IRAK1↓, Trif↓, NF-κB p65↓, p-IRF3↓, IRF3↓	Shao et al. (2016)
	Glucose 40 mM, 48 h; STZ 50 mg/kg, 5 days	MPC5; C57BL/6J	80 μM; 200 mg/kg(i.p.)	Restore autophagy	VEGF2↓, caspase 3↓, PI3K/AKT↓	Wang et al. (2022c)
DPN	STZ 150 mg/kg	ddY mice	30 mg/kg(p.o.)	Modulate spinal nociceptive transmission	Activate α2-adrenoceptors, Noradrenaline↑	Lee et al. (2011)
	Glucose 150 mM, 48 h	RSC96	100 μM	Inhibit apoptosis	Anti-oxidative stress, Nrf2/ARE↑, ROS↓, MDA↓, GST↑, GPX↑, Bcl-2↑, Bax↓, Caspase-3↓	Yang et al. (2015)
	Glucose 150 mM, 24 h	RSC96	10 μM	Restoration of mitochondrial function	Pmpca↑, Sumo1↑, Trx2↑, TrxR2↑, Prx3↑, ROS↓	Yang J. et al. (2022)
DPN	Glucose 150 mM, 24 h	SC line	100 μM	Inhibit ER stress and DRGn apoptosis	JNK↓, CHOP↓, XBP1s↑, IRE1α↓, GRP78↓, Bcl-2↑, Bax↓, Caspase-12↓, Caspase-3↓	Zhu et al. (2021)
Diabetic wounds	HG MEM, 48 h; STZ 35 mg/kg	HaCaT; SD rats	100 μM; 30 mg/kg(i.g.)	Promote proliferation and migration, Inhibit apoptosis	Anti-oxidative stress, Nrf2 pathway↑, VEGF↑, TGF-β1↑	Sun et al. (2020)

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TABLE 2 (Continued) Mechanism of PF in diabetes and complications.

Disease	Model Methods	Animal/Cell lines	Dose/Concentration	Efficacy	Mechanisms	Ref
	HG MEM, 48 h; STZ 35 mg/kg	HaCaT; SD rats	100 μ M; 30 mg/kg(i.g.)	—	Anti-Inflammatory, IL-1 β ↓, IL-18↓, TNF- α ↓, CXCR2↓, NF- κ B↓, I κ B↓, NLRP3↓, Caspase-1↓	Sun et al. (2021)
	STZ 55 mg/kg, 5 days	C57BL/6J	500 μ M, hydrogel	Promote proliferation and maturation;	Anti-Inflammatory, CD86↓, TNF- α ↓, IL-1 β ↓, iNOS↓, CD206↑, IL-10↑, TGF- β ↑, Arg-1↑, CD31↑, VEGF↑, α -SMA↑, Col-1↑	Yang et al. (2021)
	STZ 60 mg/kg	SD rats	20 mg/mL, hydrogel	Promote angiogenesis, collagen deposition;	Anti-Inflammatory, IL-10↑, TNF- α ↓, CD31↑	Guo et al. (2022)
NAFLD	HFD, 12 weeks	C57BL/6J	100 mg/kg(i.g.)	—	Anti-Inflammatory, Triglyceride↓, Cholesterol↓, AST↓, TNF- α ↓	Zhou et al. (2019)
	HFD, 10 weeks	SD rats	20 mg/kg(i.g.)	Regulate lipid metabolism	Anti-oxidative stress, TG↓, TC↓, FFA↓, FBG, ALT↓, AST↓, SOD↓, MDA↓, CYP2E1↓, ROS↓, IRS/Akt/GSK3 β	Ma et al. (2017a)
DLI	Glucose 300 mM, 24 h; —	AML12; db/db, db/m mice	16 μ M; 100 mg/kg(i.g.)	Inhibit apoptosis	Anti-Inflammatory, Anti-oxidative stress, IL-1 β ↓, IL-18↓, TNF- α ↓, F4/80↓, ROS↓, ASC↓, Caspase-1↓, TXNIP/NLRP↓	Wang et al. (2022d)
Diabetic myocardial ischemic injury	STZ 150 mg/kg	C57BL/6, TRPV1 ^{-/-} mice	140 mg/kg(i.g.)	—	TRPV1/CaMK/CREB/CGRP↑	Han et al. (2016)
	STZ 30 mg/kg	SD rats	90 mg/kg(i.g.)	Inhibit apoptosis	Anti-oxidative stress, SOD↑, MDA↑, Bax↓, Bcl-2↑, Caspase-3↓	Li et al. (2021b)
DR	Glucose 25 mM, 6 hours; STZ 60 mg/kg	BV2; CD-1 mice	10 μ M; 40 mg/kg(p.o.)	—	Anti-Inflammatory, SOCS3↑, MMP-9↓, IBA-1↓, IL-1 β ↓, TLR4/p38/NF- κ B↓	Pei et al. (2023)
	STZ 50 mg/kg	SD rats	20 mg/kg(i.g.)	Reduce blood sugar, Glial cells activation	GAFP↓, GLAST↑, GS↑	Zhang T. et al. (2019)
	STZ 50 mg/kg	SD rats	4 mg/kg(i.p.)	—	Anti-Inflammatory, GAFP↓, IL-6↓, IL-1↓, TNF- α ↓, JAK2/STAT3↓	Zhang et al. (2023a)
Diabetic vascular disease	Glucose 25 mM, 24 h; STZ 30 mg/kg	HUVECs; SD rats	100 μ M; 10 mg/kg(i.g.)	Inhibit apoptosis	Anti-Inflammatory, TNF- α ↓, PKC β 1↓	Wang et al. (2019)
	STZ 35 mg/kg	C57BL/6J	100 mg/kg(i.g.)	—	Anti-oxidative stress, ALT↓, AST↓, AGEs↓	Huang et al. (2022)
Cognitive dysfunction	STZ 35 mg/kg	SD rats	30 mg/kg(i.g.)	Inhibit tau hyperphosphorylation	Anti-Inflammatory, IL-1 β ↓, TNF- α ↓, SOCS2↓, IRS-1↑, Akt↑, GSK-3 β ↑	Sun et al. (2017)
	STZ 3 mg/kg, day 1 and 3	C57BL/6	10 mg/kg(i.p.)	Regulate mitochondrial and islet dysfunction	Anti-oxidative stress, p-Pl3K↑, p-Akt↑, p-IRS-1↓	Wang et al. (2018)
Pancreatic β -cells injury	STZ 3 mM, 24 h	INS-1	80 μ M	Inhibit apoptosis	Anti-oxidative stress, Caspase-3↓, Bax↓, Bcl-2↑, ROS↓, MDA↓, SOD↑, p-p38↓, p-JNK↓, MAPK↓	Liu C. et al. (2019)
Gestational diabetes	STZ 25 mg/kg	Albino rats	30 mg/kg(p.o.)	Reduce blood sugar	Akt/mTOR↓, p-4E-BP1↓, p-SGK1↓	Zhang et al. (2020)
	STZ 35 mg/kg	SD rats	30 mg/kg(i.g.)	Inhibit ferroptosis	ROS↓, MDA↓, GSH↑, p-PI3K↑, Akt/Nrf2/GPX4↑	Lian et al. (2023)

(Continued on following page)

TABLE 2 (Continued) Mechanism of PF in diabetes and complications.

Disease	Model Methods	Animal/Cell lines	Dose/Concentration	Efficacy	Mechanisms	Ref
Diabetic cataract	Glucose 30 mM, 24 h	SRA01/04	10 μ M	—	Inhibit EMT of lens epithelial cells, Anti-oxidative stress, E-cadherin $\uparrow$, N-cadherin $\downarrow$, Vimentin $\downarrow$, Snail $\downarrow$, SOD $\uparrow$, GSH-Px $\uparrow$, MDA $\downarrow$, Bax $\downarrow$, c-caspase 9 $\downarrow$, cytochrome c $\downarrow$, Bcl-2 $\uparrow$, SIRT1 $\uparrow$	Zeng et al. (2022)
Diabetic periodontitis	STZ 50 mg/kg	Wistar rats	100 mg/kg(i.g.)	Reduce bone loss, enhance bone quality	Anti-Inflammatory, IL-1 β $\downarrow$, IL-6 $\downarrow$, TNF- α $\downarrow$	Kuzu et al. (2023)

TABLE 3 Mechanism of PF extract and compound in Diabetes and Complications.

Disease	Model methods	Animal/Cell lines	Dose/Dosing method/period	Efficacy	Mechanisms	Ref
Diabetes	HFD 20 weeks	C57BL/6N	SYT 400 mg/kg (i.g.)	Suppress liver lipogenesis	Anti-Inflammatory, TNF- α $\downarrow$, IL-4 $\downarrow$, IL-6 $\downarrow$	Yao et al. (2021)
	—	db/db mice	PFExt 200 mg/kg (i.g.)	Reduce blood sugar	—	Chang et al. (2016)
	—	db/db mice	EAF 100 mg/kg (i.g.)	Reduce blood sugar	Anti-Inflammatory, Anti-oxidative stress, SOD $\uparrow$, Catalase $\uparrow$, MDA $\downarrow$, ROS $\downarrow$	Zhang et al. (2023a)
DN	STZ 65 mg/kg	Wistar rats	TGP 200 mg/kg (p.o.)	—	Anti-Inflammatory, Anti-oxidative stress, Col-VI $\downarrow$, ICAM-1 $\downarrow$, IL-1 $\downarrow$, TNF- α $\downarrow$, NF- κ B p65 $\downarrow$, 3-NT $\downarrow$, nephrin protein $\uparrow$, TGF- β 1 $\downarrow$	Wu et al. (2009)
	STZ 30 mg/kg	SD rats	MC-TG 808 mg/kg (i.g.)	Ameliorate ER stress-related inflammation	Anti-Inflammatory, GRP78/Bip $\downarrow$, XBP-1(s) $\downarrow$, MCP-1 $\downarrow$, ICAM-1 $\downarrow$, p-IRF3 $\downarrow$, NF- κ B p-p65 $\downarrow$	Chen et al. (2016)
	STZ 65 mg/kg	Wistar rats	TGP 200 mg/kg (p.o.)	—	Anti-Inflammatory, JAK/STAT3 $\downarrow$	Wang et al. (2012)
	STZ 65 mg/kg	Wistar rats	TGP 200 mg/kg (p.o.)	—	Anti-Inflammatory, α -SMA $\downarrow$, E-cad $\uparrow$, TLR2 $\downarrow$	Zhang et al. (2014)
DPN	STZ 60 mg/kg	SD rats	TLN 21.8 g/kg (i.g.)	Improve neurological function	Anti-oxidative stress, TAOC $\uparrow$, ROS $\downarrow$, Nrf2 $\uparrow$, γ GCS $\uparrow$, Bcl2 $\uparrow$, Bax $\downarrow$, Cyto C $\downarrow$	Ji et al. (2016)
	STZ 60 mg/kg	SD rats	TGP 5.6 mg/kg (i.g.)	Restore mitochondrial function	Pmpca $\uparrow$, Sumo1 $\uparrow$, Trx2 $\uparrow$, TrxR2 $\uparrow$, Prx3 $\uparrow$, ROS $\downarrow$	Yang X. et al. (2022)
Diabetic wounds	STZ 35 mg/kg	SD rats	3% PF-SA-gelatin, skin scaffolds	Promote angiogenesis, collagen deposition	Anti-Inflammation, IL-1 β $\downarrow$, CD31 $\uparrow$	Yu et al. (2022)
DLI	—	H4IIE	PR-Et 400 mg/kg	Reduce blood sugar	PEPCK $\downarrow$	Juan et al. (2010)
Diabetic myocardial fibrosis	STZ 40 mg/kg, 2 days	Wistar rats	SSYX 200 mg/kg	Inhibit cardiac fibrosis	Anti-Fibrosis, TGF- β 1 $\downarrow$, Col-I $\downarrow$, Col-III $\downarrow$, MMP-2 $\downarrow$, MMP-9 $\downarrow$, α -SMA $\downarrow$, p-Smad2/3 $\downarrow$, Smad7 $\uparrow$	Shen et al. (2014)
Glycemic variability	Glucose 25 mM, 24 h STZ 30 mg/kg	HUVECs; SD rats	PAE 100 μ M PAE 10 mg/kg (i.g.)	Platelet activation	Anti-oxidative stress, CD62p $\downarrow$, ROS $\downarrow$, GSH-px $\uparrow$	Huang et al. (2020)

mediators. These factors activate signaling pathways such as c-Jun N-terminal kinase (JNK) and I κ B kinase, disrupting insulin receptor substrate (IRS) function and impairing insulin signaling (Tang et al., 2021). Additionally, inflammation directly damages pancreatic β -cells, triggering apoptosis and pyroptosis, ultimately leading to reduced insulin secretion. Recent findings highlight the pivotal role of the NLRP3 inflammasome in diabetes progression. Hyperglycemia and dyslipidemia stimulate NLRP3 activation *via*

reactive oxygen species (ROS), promoting inflammatory responses and β -cell pyroptosis, thereby worsening glucose metabolism dysregulation (Radmehr et al., 2025).

Oxidative stress further exacerbates diabetes pathogenesis by generating excess ROS through glucose autooxidation and the formation of advanced glycation end products (AGEs) (Khalid et al., 2022). Elevated ROS levels not only damage β -cells but also activate stress kinases that interfere with insulin signaling, aggravating insulin resistance. Notably, inflammation and oxidative stress reinforce each other, creating a self-perpetuating cycle where inflammation induces ROS production, and oxidative stress amplifies inflammatory signaling. Emerging research has explored therapeutic strategies targeting these mechanisms, including peroxisome proliferator-activated receptor (PPAR) modulators to mitigate insulin resistance and inflammation (Qiu et al., 2023). Additionally, interventions such as NLRP3 inflammasome inhibitors, antioxidants, and gut microbiota modulation are gaining attention for their potential in diabetes prevention and treatment. Understanding the intricate interplay between inflammation and oxidative stress may pave the way for novel therapeutic approaches to improve diabetes management.

2.6 Self-immune response and genetic factors

The self-immune response is the body's immune response to its own tissues, including the autoimmune attack on pancreatic β -cells, which is the main pathogenic mechanism of T1D (Nakayasu et al., 2023). Genetic factors largely determine an individual's susceptibility to diabetes, especially T2D (Velloso et al., 2013).

T1D is an autoimmune-mediated disease characterized by the autoimmune destruction of pancreatic β -cells, resulting in severe insulin deficiency. Studies have shown that various autoantibodies, such as islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GADA), insulin antibodies (IAA), and unique self-immune responses like T-cell-mediated immune responses, are associated with the onset of T1D (Ilonen et al., 2019). These self-immune responses lead to a gradual reduction of pancreatic β -cells and decreased insulin secretion, thereby causing hyperglycemic symptoms. However, the genetic susceptibility of T2D is particularly evident. Numerous familial and twin studies have shown that the risk of developing T2D is closely related to genetic factors. Multiple gene variants associated with an increased risk of T2D have been discovered, including TCF7L2, PPARG, KCNJ11, etc (Sanghera et al., 2010; Bonnefond et al., 2020; Mansour Aly et al., 2021). These gene variants affect key physiological processes such as insulin secretion, insulin signaling pathways, pancreatic β -cell function, and energy metabolism, thereby increasing the risk of developing T2D.

Genetic factors not only influence the risk of diabetes onset but also affect the clinical manifestations, complications risk, and treatment response of diabetes. Different gene mutations can lead to varied pancreatic β -cell functions and insulin sensitivities, thereby affecting the clinical manifestations and treatment needs of diabetes. At the same time, some gene mutations are closely related to the risk of diabetes complications, such as cardiovascular disease, kidney disease, and eye diseases.

2.7 Lifestyle and environment

In contemporary society, the enhancement of living standards and the rapid pace of life have led to an increase in unfavorable lifestyle factors contributing to the rising prevalence of diabetes, including obesity, irregular dietary habits, physical inactivity, and psychological stress.

Obesity and poor dietary habits stand as predominant risk factors for T2D. The swift tempo of modern urban life facilitates the easy access and consumption of high-sugar, high-fat, and high-calorie foods. Prolonged irregular eating patterns result in fat accumulation, consequently expediting the development of insulin resistance and the onset of T2D (Ladher et al., 2023). Furthermore, consistent physical exercise not only aids in weight management but also improves the body's insulin sensitivity, thereby promoting stable blood sugar levels and reducing the risk of diabetes.

Psychological stress and shifts in lifestyle habits are equally pivotal factors influencing diabetes onset. The escalating competitive pressures in today's society can induce chronic emotional strain and mental stress, leading to disruptions in the endocrine system and elevated blood sugar levels, thus hastening the progression of insulin resistance and diabetes (Ghosh et al., 2020). The rapid pace of modern life, coupled with excessive reliance on motor vehicles, sedentary behaviors, and limited physical activity, fosters detrimental lifestyle habits that contribute to diabetes onset.

Environmental factors are also instrumental in the development and progression of diabetes (Xie et al., 2022). Prolonged exposure to specific chemicals, such as organic mercury and pesticides, has been associated with an elevated risk of diabetes. Moreover, air pollution, particularly extended exposure to fine particulate matter such as PM_{2.5}, correlates with an increased risk of diabetes onset and challenges in blood sugar regulation. These environmental pollutants not only intensify the onset of diabetes but also exacerbate the condition and elevate the risk of complications in individuals with diabetes. In brief, the pathogenesis of diabetes involves multiple factors as shown in Figure 2.

3 Pharmacological activities of PF

3.1 Diabetes

Diabetes, a chronic metabolic disease caused by insufficient insulin secretion or insulin resistance, characterized primarily by high blood sugar levels (Cole and Florez, 2020). Diabetes is divided into T1D and T2D. T1D is an autoimmune disease resulting from impaired insulin secretion, while T2D is mainly due to insulin resistance and dysfunction of pancreatic β -cells (Hu J. et al., 2023).

Tables 2, 3 summarized the pharmacological effects of PF, along with its extracts, in diabetes mellitus and related complications. PF has gained widespread attention in recent years due to its significant hypoglycemic effects. Studies have shown that PF can enhance glucose utilization, significantly reduce blood glucose levels, and achieve maximum effects 25 min after treatment (Hsu et al., 1997). Another study found that the alcohol extract of *Radix Paenoniae Alba* (RPA) can significantly reduce fasting blood glucose levels in db/db mice and bring them to levels similar to C57/B6 mice after 30 days.

Furthermore, it effectively improves glucose intolerance, Homeostasis Model Assessment (HOMA) index, *in vivo* glucose uptake, reduces body weight, and alleviates hepatic steatosis (Chang et al., 2016). Importantly, the hypoglycemic effect of PF is independent of insulin action.

Research has found that PF can protect NOD mice from the effects of T1D by modulating the gut microbiota and inhibiting the Toll-like receptor 4 (TLR4)-myeloid differentiation primary response protein 88/TIR-domain-containing adapter-inducing interferon- β (MyD88/TRIF) pathway (Zhu et al., 2017). Additionally, a novel anti-diabetic monomer combination (AMC) has been proven to have significant therapeutic effects on high-fat diet (HFD)-induced Type 2 diabetic mice, and its mechanism of action may involve the regulation of bacterial-co-metabolism-inflammatory responses (Han et al., 2020). Sanye Tablet (SYT) is a patented prescription drug rich in PF and widely used for the treatment of T2D and prediabetes. Research has found that SYT can improve lipid metabolism and insulin sensitivity by inhibiting liver lipid synthesis pathways, such as down-regulating Sterol Regulatory Element-Binding Protein 1/Acetyl-CoA Carboxylase (SREBP1/ACC) and Janus Kinase/Transducer and Activator of Transcription (JAK/STAT) signaling pathways, and by modulating the JAK-STAT pathway through its effects on Proviral Integration site for Moloney murine leukemia virus 2 (PIM2) and STAT1 (Chen et al., 2017). Furthermore, the ethyl acetate extract (EAF) of RPA has significant antioxidant and hypoglycemic activities (Zhang et al., 2023c). Overall, PF has a remarkable hypoglycemic effect and may exert its therapeutic effects through various mechanisms, including enhancing insulin secretion, improving insulin resistance, modulating gut microbiota, and antioxidant activities.

3.2 DN

DN is kidney damage caused by diabetes mellitus and is a prevalent complication in diabetic patients (Hu Q. et al., 2023). As diabetes progresses, the glomerular filtration rate decreases, microalbuminuria and proteinuria develop, and may eventually lead to chronic renal failure (Alicic et al., 2017). A large number of studies have confirmed that nephropathy mitigates the effects of PF by inhibiting the inflammatory response, reducing oxidative damage of mesangial cells induced by AGEs, up-regulating autophagy activity and immunomodulation (Figure 3). These cascading events require co-regulation of the multifarious cellular signaling pathways such as JAK2/STAT3 pathway, TLR2/4 pathway, Receptor for Advanced Glycation End products/mammalian target of rapamycin signaling (RAGE/mTOR) pathway, Phosphatidylinositol 3-kinase/Protein Kinase B (PI3K/AKT) pathway, Plant Inositol Phosphate Kinase (PIPK1/PIPK3) pathway, Silent information regulator of transcription 1/Nuclear factor erythroid 2-related factor 2/Nuclear factor kappa B (SIRT1/Nrf2/NF- κ B) pathway (Fu et al., 2009; Wu et al., 2009; Wang et al., 2012; Zhang et al., 2014; Chen et al., 2016; Sun et al., 2017; Shao et al., 2017; Zhang et al., 2017; Shao et al., 2019; Wang et al., 2022a).

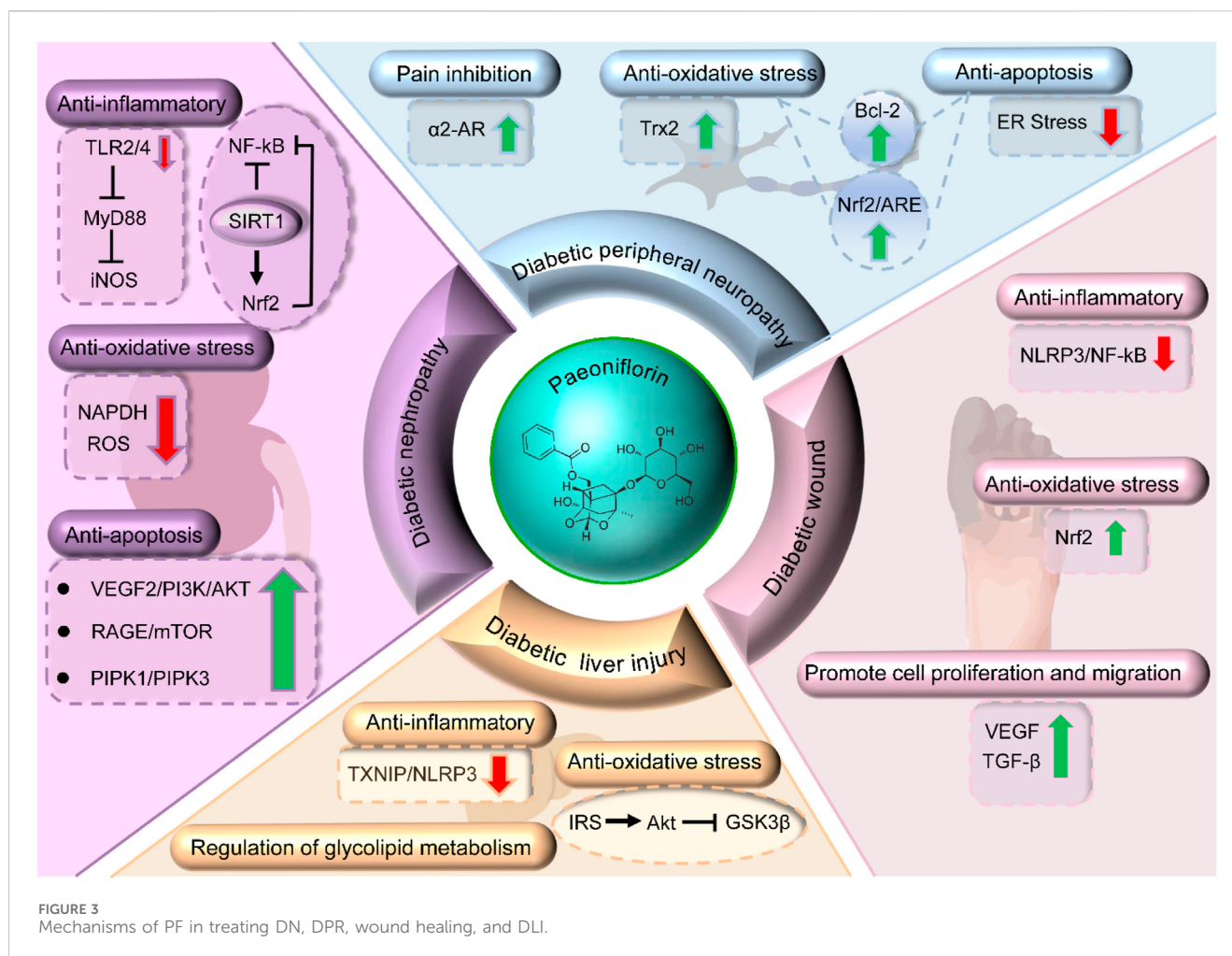
The study showed that PF and oxyphaeniflora were able to attenuate AGEs-induced oxidative damage and inflammation in mesangial cells, thereby improving DN (Zhang et al., 2013). *In vitro*

studies, PF reduced the activity of nicotinamide-adenine dinucleotide phosphate oxidase (NADPH), and decreased the level of ROS, transforming growth factor- β 1 (TGF- β 1) and fibronectin in high glucose cultured mesangial cells (Sun et al., 2015). Although the anti-inflammatory efficacy of PF has been well illustrated in several animal models, whether it could attenuate DN and detailed mechanisms are still obscure. The current study suggested that high glucose activates macrophages primarily through TLR2-dependent mechanisms which aggravated the severity of renal inflammation and eventually contributed to DN. Shao et al. confirmed that PF suppressed HG-induced production of TLR2, activation of downstream signaling and synthesis of inducible nitric oxide synthase (iNOS), and it further inhibited the MyD88-dependent pathway (Shao et al., 2016).

Furthermore, PF has been proven to attenuate AGEs-induced mesangial cell damage, but the regulatory mechanism of autophagy remains unclear. Chen et al. further demonstrated that PF inhibits AGEs-induced mesangial cell dysfunction, at least in part, by inhibiting RAGE and up-regulating p-mTOR levels, thereby inhibiting autophagy and ameliorating DN (Ma et al., 2017a). However, the mechanism of autophagy regulation exerted by PF is also completely different in different cell lines. In MCP5 cells, Wang et al. demonstrated that PF can restore podocyte autophagy and inhibit apoptosis by targeting Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)-mediated the PI3K/AKT pathway to improve DN injury. In addition, VEGFR2 as a target of PF can directly bind to it by molecular docking and surface plasmon resonance detection, which provides a new theoretical basis for PF treatment of DN (Wang et al., 2022b).

3.3 Diabetic peripheral neuropathy (DPN)

Among diabetic patients, DPN is prevalent and is characterized by symptoms such as neuralgia, sensory abnormalities, and motor disorders (Hammad et al., 2020; Jensen et al., 2021; Wang et al., 2023b). Recent research suggests that PF, holds promise for DPN treatment. Relevant studies indicate that PF exerts therapeutic effects on DPN through various mechanisms (Lee et al., 2011; Ji et al., 2016). Initially, by activating spinal Alpha-2 adrenergic receptor (α 2-AR), PF significantly elevates the pain threshold in diabetic rats, thus alleviating pain sensation (Yang et al., 2015). This discovery provides crucial theoretical underpinnings for employing PF in clinical settings to alleviate DPN-associated pain. Studies have shown that PF can effectively alleviate oxidative stress in Schwann cells induced by high glucose by regulating Nrf2/ARE pathway and Bcl-2-related apoptotic pathway (Yang et al., 2016). Moreover, PF enhances nervous system function in diabetic rats by modulating the expression of mitochondrial thioredoxin (Trx2). Research has shown that PF upregulates Trx2 expression and its associated proteins, diminishes mitochondrial oxidative stress, and consequently mitigates nerve system damage in DPN patients (Yang Y. et al., 2022). Furthermore, PF mitigates nerve cell apoptosis by regulating the endoplasmic reticulum stress pathway, thereby providing additional protection against high glucose-induced nervous system damage (Zhu et al., 2021). Nevertheless, despite evidence of PF's multifaceted therapeutic effects, its precise mechanism of action remains incompletely



understood, necessitating further research to elucidate its molecular mechanisms.

3.4 Diabetic wound

Diabetic foot ulcers (DFU) currently pose significant challenges in treatment, with potential severe outcomes including limb ischemia or amputation (Armstrong et al., 2017; Armstrong et al., 2023). PF, possessing biologically active properties such as antioxidants and anti-inflammatory effects, has garnered significant interest (Song et al., 2017; Wen et al., 2019; Zhou et al., 2020; Li et al., 2022; Ren et al., 2023). Research indicates that PF enhances wound healing in diabetic rats by activating the Nrf2 pathway. Consequently, this activation reduces oxidative stress necessary for wound healing, enhances cell proliferation and migration, reduces apoptosis, and upregulates the expression of VEGF and TGF-β1 (Sun et al., 2020). Furthermore, PF can suppress the inflammatory response mediated by NLRP3 and NF-κB, consequently mitigating DFU inflammation and facilitating the healing process (Sun et al., 2021). Recently, there has been a surge in research interest in encapsulating PF in various hydrogels or skin scaffolds for treating DFU. Such encapsulation

has demonstrated efficacy in hemostasis, antibacterial activity, modulation of macrophage polarization, inflammation reduction, enhancement of angiogenesis and epithelialization, and promotion of collagen deposition, thereby effectively fostering wound healing (Yang et al., 2021; Guo et al., 2022; Yu et al., 2022). These findings offer crucial experimental validation for the therapeutic potential of PF in managing DFU.

3.5 Diabetic liver injury (DLI)

Individuals with diabetes commonly experience DLI, marked by hepatic steatosis, inflammation, and aberrant liver function (Rao et al., 2021; Wang et al., 2023; Thoudam et al., 2023). DLI can result in severe outcomes, including cirrhosis, liver dysfunction, and potentially liver cancer, significantly reducing patients' quality of life (Hoofnagle and Björnsson, 2019; Newman et al., 2019; Long et al., 2022). PF exhibits therapeutic potential for diabetic liver disease by inhibiting gluconeogenesis, modulating lipid metabolism, the insulin signaling pathway, and suppressing inflammatory responses (Ma et al., 2017b; Li et al., 2018a; Shu et al., 2019; Zhang et al., 2022b; Wang et al., 2022c; Liu et al., 2023b). Studies indicate that PF reduces blood glucose levels in diabetic rats and db/

db mice by inhibiting PEPCK transcription (Juan et al., 2010). Additionally, PF exhibits therapeutic potential for non-alcoholic fatty liver disease (NAFLD) (Zhou et al., 2019). A study suggested that PF inhibits ectopic lipid deposition by modulating lipid metabolism (specifically inhibiting cholesterol synthesis and the *de novo* pathway) and enhancing insulin sensitivity via the IRS/Akt/GSK3 β insulin signaling pathway and antioxidant mechanisms (Ma et al., 2017c). A recent study validated that PF's reversal of abnormal liver function and hepatic steatosis in db/db mice is linked to the inhibition of the TXNIP/NLRP3 signaling pathway, indicating TXNIP as a possible target of PF (Wang et al., 2022d). In conclusion, PF exhibits promising therapeutic potential for diabetic liver injury and non-alcoholic fatty liver disease through the modulation of multiple signaling pathways and molecular mechanisms. Further research is warranted to elucidate its therapeutic mechanisms and to conduct clinical trials assessing its efficacy and safety in diabetic patients.

3.6 Diabetic myocardial ischemic injury

Characterized by myocardial fibrosis, inflammatory responses, and impaired cardiac function, diabetic myocardial injury is a prevalent complication in diabetic patients (Figure 4) (Gan et al., 2020; Yu et al., 2021; Wu et al., 2023). Shensong Yangxin Capsule (SSYX), a traditional Chinese herbal medicine abundant in PF, has been extensively used in China for treating arrhythmias. Research indicates that SSYX can mitigate the fibrosis associated with diabetic cardiomyopathy by suppressing the TGF- β 1/Mothers against decapentaplegic homolog (Smad) signaling pathway (Shen et al., 2014). Investigations into the therapeutic mechanisms of PF for diabetic myocardial injury predominantly center on its neuroprotective properties and its impact on ischemic heart disease. Notably, PF has been observed to safeguard diabetic mice from myocardial ischemic injury by modulating the transient receptor potential vanilloid 1 (TRPV1)/calcitonin gene-related peptide signaling pathway (Han et al., 2016). Moreover, PF regulates glycolipid metabolism in T2DM model rats, bolsters their antioxidant defenses, suppresses myocardial cell apoptosis, and exhibits a discernible therapeutic effect on myocardial injury (Li et al., 2021b).

3.7 Diabetic retinopathy (DR)

DR often leads to vision impairment (Yue et al., 2022; Bryl et al., 2022). Existing research indicates that inflammation of retinal microglial cells is instrumental in the progression of DR (Zhang Y. et al., 2019). Notably, matrix metalloproteinase 9 (MMP-9) in these cells critically compromises the integrity of the blood-retinal barrier and regulates inflammatory processes (Beltramo et al., 2023). Recent studies have demonstrated that PF suppresses the TLR4/NF- κ B signaling pathway by enhancing the expression of suppressor of cytokine signaling 3 (SOCS3), leading to a decrease in MMP-9 expression and inflammatory reactions in retinal microglial cells exposed to high glucose (Tu et al., 2019; Fan et al., 2020; Pei et al., 2023). A study suggested that PF could safeguard Müller cells in diabetic rat retinas by upregulating the expression of L-glutamate/

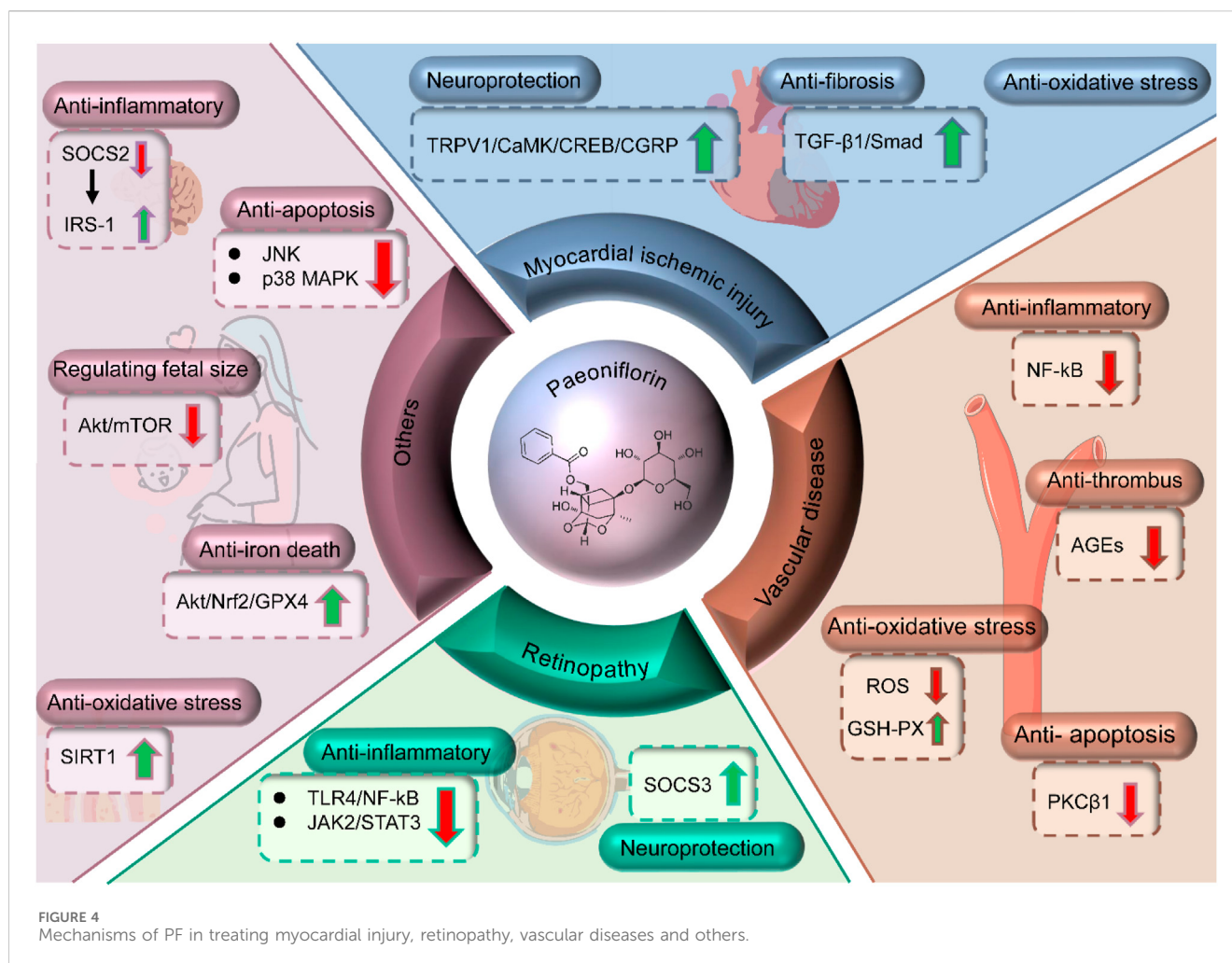
L-aspartate transporter (GLAST) and glutamine synthase (GS) (Zhang B. et al., 2019). Subsequently, the research group further highlighted that PF effectively attenuates neuroinflammation in the retinal cells of diabetic rats through the inhibition of the JAK2/STAT3 signaling pathway (Zhang et al., 2023d). Collectively, PF demonstrates pronounced therapeutic potential against diabetic retinopathy by suppressing inflammation, modulating cellular signaling, and reducing blood glucose levels.

3.8 Diabetic vascular disease

Diabetes-related vascular complications frequently manifest in diabetic patients. The underlying pathogenesis is predominantly linked to sustained hyperglycemia, endothelial cell impairment due to fluctuations in blood glucose, elevated oxidative stress, and platelet activation (Mohammedi et al., 2015; Yeom et al., 2016; Liu C. et al., 2019; SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration, 2023). PF, with its anti-apoptotic, anti-inflammatory, and anti-thrombotic properties, offers substantial protection against cardiovascular and cerebrovascular disorders. Studies have demonstrated that PF can mitigate oxidative stress, diminish inflammatory reactions, and decrease the Protein kinase C beta 1 (PKC β 1) protein expression, thus mitigating damage to human umbilical vein endothelial cells (HUVECs) caused by elevated glucose levels (Wang et al., 2019). In diabetic rat models, PF has proven protective against vascular damage. Furthermore, PF has notable effects in suppressing oxidative stress and platelet activation. It enhances the morphology and viability of HUVECs influenced by glycemic fluctuations, diminishes platelet aggregation, reduces ROS concentrations, and elevates Glutathione peroxidase (GSH-px) levels (Huang et al., 2020). Notably, combined administration of PF and metformin in diabetic rats significantly lowers blood glucose, Alanine Aminotransferase (ALT), and Aspartate Aminotransferase (AST) levels and substantially decreases AGEs, underscoring the therapeutic potential of PF against diabetic vascular complications (Huang et al., 2022). Nevertheless, research investigating the combined therapeutic effects of PF with other conventional antidiabetic medications remains limited, warranting further exploration into their synergistic efficacy and mechanisms.

3.9 Others

The therapeutic efficacy of PF in alleviating diabetes-related cognitive dysfunction is well-established. In diabetic rat models, PF ameliorates cognitive impairment by modulating the Suppressor of Cytokine Signaling 2 (SOCS2)/IRS-1 signaling pathway. This enhancement correlates with PF's capacity to reduce brain inflammatory cytokines, downregulate SOCS2 expression, and boost IRS-1 activity (Sun et al., 2017). Furthermore, PF exhibits neuroprotective properties against cognitive deficits induced by intracerebroventricular (ICV) administration of Streptozotocin (STZ) (Zhang et al., 2020). PF treatment markedly ameliorates STZ-induced mitochondrial dysfunction, augments synaptic density in the hippocampal Cornu Ammonis one region, and improves cerebral insulin signaling by elevating p-PI3K and



p-Akt protein levels (Wang et al., 2018). In the context of pancreatic β-cells, PF mitigates STZ-induced apoptosis and safeguards β-cells from STZ-mediated damage by inhibiting the p38 mitogen-activated protein kinase (MAPK) and JNK pathways (Liu Y. et al., 2019). These findings suggest that PF might serve as a natural anti-diabetic agent by alleviating β-cell injury.

Concerning gestational diabetes mellitus (GDM), PF demonstrates potential therapeutic benefits. Research indicates that PF significantly ameliorates blood glucose, leptin, and insulin concentrations and curbs the hyperactivation of the Akt/mTOR signaling in placental tissue. This normalization contributes to fetal size and weight regulation in GDM-affected rats (Zhang et al., 2020). A recent investigation highlighted the protective role of PF in pancreatic tissue of GDM rats, potentially *via* the Akt/Nrf2/GPX4 pathway to counter ferroptosis (Lian et al., 2023). Additionally, PF confers protection against diabetic cataracts. Under hyperglycemic conditions, it substantially enhances the viability of human lens epithelial SRA01/04 cells and suppresses epithelial-mesenchymal transition (EMT) and oxidative damage by upregulating SIRT1 expression (Zeng et al., 2022). In a diabetic periodontitis model, PF demonstrated significant anti-inflammatory effects by reducing pro-inflammatory cytokines, leading to decreased bone loss. Micro-CT analysis further revealed that PF treatment enhanced bone quality by increasing bone mineral density

and improving trabecular number and thickness. These results indicate that PF may have potential therapeutic value in managing diabetic periodontitis, particularly through its anti-inflammatory properties and role in preserving bone integrity (Kuzu et al., 2023).

In summary, as a natural monoterpene glycoside, PF presents a multi-faceted therapeutic potential for diabetes and its associated complications. Nevertheless, despite the promising initial findings, further clinical investigations are imperative to validate its safety, efficacy, and elucidate its mechanisms of action.

4 Pharmacokinetics of PF

PF, a tetracyclic glycoside predominantly found in plants of the *Paeaniaceae* family, such as white peony and red peony. Upon entering the human body, peony glycoside quickly reaches the bloodstream *via* routes like oral administration or injection. Following gastrointestinal absorption, it distributes widely in body tissues, including crossing the blood-brain barrier and the placenta (Hu et al., 2016; Wu et al., 2022). In the body, the primary metabolism of peony glycoside occurs in the liver through enzymatic processes, leading to the formation of metabolites that are subsequently excreted by the kidneys (Mei et al., 2023).

After oral administration, PF is rapidly absorbed from the gastrointestinal tract. The absorption process is generally considered to be efficient but may be affected by the presence of other components in the herb or food. It has been reported that PF undergoes passive diffusion across the intestinal membrane (Luo C. et al., 2023). The bioavailability of PF is relatively high, suggesting that it can reach therapeutic concentrations in the bloodstream after oral administration. Once absorbed into the bloodstream, PF is distributed to various tissues and organs. It has a relatively large volume of distribution, indicating that it is extensively distributed in the body. PF is predominantly distributed in the liver, kidneys, and spleen, which are important target organs for its therapeutic effects in diabetes. It is also found in the plasma, where it binds to plasma proteins to some extent (Li et al., 2018b; Li Y. et al., 2023). The distribution of PF to the target organs is essential for its pharmacological action against diabetes. Additionally, PF undergoes extensive metabolism in the liver. The primary metabolic pathway involves hydrolysis of the glucoside bond to form PF aglycone and glucose (Hua et al., 2023). The aglycone can further undergo phase II metabolism, including glucuronidation and sulfation, to form water-soluble metabolites that are excreted in the urine. The metabolism of PF is relatively rapid, with a short half-life, indicating that it may require multiple dosing to maintain therapeutic concentrations in the bloodstream. The primary route of excretion for PF and its metabolites is through the kidneys. Renal excretion accounts for the elimination of the majority of the administered dose within 24 h (Shao et al., 2017). A smaller portion of the dose may also be excreted in the feces. The elimination of PF is relatively rapid, with a clearance rate that is proportional to renal function (Zhai et al., 2016; Chen et al., 2021). Therefore, patients with impaired renal function may require dose adjustment to prevent drug accumulation and potential toxicity.

The pharmacokinetics of PF are characterized by rapid absorption, extensive distribution, rapid metabolism, and renal excretion. Understanding these pharmacokinetic properties is essential for optimizing the therapeutic use of PF in the treatment of diabetes. Further studies are needed to investigate the potential interactions of PF with other drugs and its pharmacokinetics in special populations, such as elderly patients and those with renal impairment.

5 Toxicology of PF

Acute toxicity studies have demonstrated that PF exhibits low toxicity (Cai et al., 2021). In rodents, the oral median lethal dose (LD50) is notably high, with rats showing an LD50 of 14.55 g/kg, suggesting a wide safety margin. Even at high oral doses, such as 3 g/kg, no significant adverse reactions or fatalities were observed in animal models (Yu et al., 2022). Additionally, subacute and chronic toxicity studies have been performed to evaluate the long-term effects of PF. Results demonstrate that therapeutic doses (100–400 mg/kg) are generally well tolerated (Zhong et al., 2023). Prolonged use does not lead to significant toxicity or damage to major organs, including the liver and kidneys (Ngo et al., 2019). However, further studies are necessary to explore potential long-term risks, particularly regarding reproductive health, developmental effects, and carcinogenicity.

Genotoxicity and mutagenicity studies were conducted to assess the potential DNA-damaging effects of PF. The results of these studies were generally negative, indicating that PF does not induce significant genetic mutations or chromosomal aberrations (Liu et al., 2006). These findings support the safety of PF in human therapeutic applications. Safety pharmacological studies have confirmed that PF does not produce notable adverse effects on the cardiovascular, respiratory, and central nervous systems (Wang et al., 2016). However, caution should be exercised when administering PF concomitantly with other medications that may affect these systems.

In summary, PF exhibits a favorable toxicological profile with low acute toxicity, minimal subacute and chronic toxicity, and no genotoxic or mutagenic effects. However, continuous monitoring and further studies are necessary to fully elucidate the long-term safety and potential interactions of PF in clinical use.

6 Discussion and prospect

Current treatments for diabetes primarily include metformin, sulfonylureas, GLP-1 receptor agonists, DPP-4 inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors. These drugs regulate blood glucose through various mechanisms. Metformin reduces hepatic glucose output and improves insulin sensitivity (LaMoia and Shulman, 2021), sulfonylureas stimulate insulin secretion from pancreatic β -cells (Lv et al., 2020), GLP-1 receptor agonists and DPP-4 inhibitors enhance incretin activity, and SGLT2 inhibitors lower glucose levels by reducing renal glucose reabsorption (Xie et al., 2023). Despite their efficacy, long-term use of these drugs is associated with limitations such as gastrointestinal discomfort, hypoglycemia, and unresolved safety concerns, necessitating the exploration of alternative therapies.

Natural compounds have gained increasing attention as potential antidiabetic agents due to their multi-target effects and lower incidence of adverse reactions. Among them, plant-derived compounds such as berberine, fenugreek, and baicalin have shown promising hypoglycemic properties. Berberine enhances insulin sensitivity, reduces hepatic glucose production, and modulates gut microbiota by activating the AMP-activated protein kinase (AMPK) pathway (Qin et al., 2020). Fenugreek, rich in saponins and dietary fiber, lowers glucose absorption, enhances insulin secretion, and improves insulin sensitivity (Luo W. et al., 2023). Baicalin exerts antidiabetic effects through its anti-inflammatory, antioxidant, and glucose metabolism-regulating properties (Pan et al., 2021). Compared with these natural compounds, PF demonstrates broader metabolic regulatory potential. In addition to improving insulin resistance, PF protects pancreatic β -cells through anti-inflammatory and antioxidant mechanisms, modulating key pathways such as Nrf2/ARE, NF- κ B, and the NLRP3 inflammasome to mitigate oxidative stress and inflammation (Table 1). Furthermore, PF exhibits therapeutic potential in diabetes-related complications, including DN, DNP, and cardiovascular disorders. However, its clinical translation is hindered by poor bioavailability, limiting its therapeutic efficacy.

To overcome this challenge, future research should focus on optimizing PF's pharmacokinetic properties. Nanotechnology-based strategies, such as nanoemulsions, liposomes, and biopolymer conjugation, could enhance its stability and

absorption. Additionally, prodrug development may improve its *in vivo* bioavailability. Given that most current studies are limited to cell cultures and rodent models, more clinically relevant models—such as diabetic large animals and humanized diabetic mice—are needed to better reflect the complexity of human diabetes. Advances in omics technologies, including proteomics, metabolomics, and bioinformatics, can facilitate a deeper understanding of PF's molecular mechanisms and identify novel therapeutic targets. Furthermore, Clustered Regularly Interspaced Short Palindromic Repeats - CRISPR-associated protein 9 (CRISPR-Cas9) gene editing may provide valuable insights into its precise regulatory pathways.

Despite its promising profile, the long-term safety of PF remains insufficiently characterized. While preclinical studies suggest a favorable safety profile, comprehensive toxicological assessments are necessary before clinical application. Future clinical trials should focus on evaluating its tolerability, optimal dosing, and potential drug interactions in diabetic patients. Additionally, determining the most effective administration route—whether oral, injectable, or transdermal—will be crucial for maximizing therapeutic outcomes.

In conclusion, PF holds significant promise in diabetes management due to its multi-target mechanisms and potential benefits in preventing complications. To facilitate its clinical translation, future studies should integrate advanced drug delivery systems, omics-based analyses, and rigorous clinical trials to optimize its pharmacokinetic profile and ensure safety. These efforts will not only enhance our understanding of PF's therapeutic potential but may also contribute to the development of novel strategies for diabetes and other metabolic disorders.

Author contributions

XO: Writing – original draft. ZY: Writing – review and editing. CP: Writing – review and editing. XZ: Investigation, Writing – review and editing. DL: Formal Analysis,

Writing – review and editing. ZQ: Validation, Writing – review and editing. XZ: Funding acquisition, Project administration, Supervision, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Chongqing Clinical Pharmacy Key Specialties Construction Project, the Science and Technology Research Program of Chongqing Municipal Education Commission (Grant No. KJQN202400133).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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