

OPEN ACCESS

EDITED BY

Weicheng Hu,
Yangzhou University, China

REVIEWED BY

Bin-Nan Wu,
Kaohsiung Medical University, Taiwan
Qiong-Yao He,
Huazhong University of Science and
Technology, China

*CORRESPONDENCE

Xiaoyuan Zheng,
✉ XiaoyuanZheng20@126.com

† These authors have contributed equally to
this work

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

COPYRIGHT

© 2025 Ou, Yu, Pan, Zheng, Li, Qiao and Zheng.

This is an open-access article distributed under
the terms of the [Creative Commons Attribution
License \(CC BY\)](#). The use, distribution or
reproduction in other forums is permitted,
provided the original author(s) and the
copyright owner(s) are credited and that the
original publication in this journal is cited, in

accordance with accepted academic practice.

No use, distribution or reproduction is
permitted which does not comply with these terms.

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

Xue Ou[†], Zhijie Yu[†], Chuanyu Pan, Xi Zheng, Dandan Li,
Zhenzhen Qiao and Xiaoyuan Zheng*

Pharmacy Department, Chongqing Emergency Medical Center, Chongqing University Central Hospital,
School of Medicine, Chongqing University, Chongqing, China

The escalating global prevalence of diabetes underscores the urgency of addressing its treatment and associated complications. Paeoniflorin, a monoterpene 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 no longer pose a 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, and the structural limits of a toothpick bridge, 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; Gorgogietasetal., 2023).

Recently, natural products have increasingly been spotlighted as potential novel strategies for diabetes and its complications' treatment (Yang X. et al., 2022; Wan 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 effect on pancreatic β -cells, and amelioration of diabetic complications (Luo W. et al., 2023; Lian 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; Zhan et al., 2023a; Zhan 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 (Zhan 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 DeVito, 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 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

(Continued on following page)

TABLE1(Continued)Listofabbreviationsandthecorrespondingfull terms.

Abbreviation	Fullterms
FBG	Fastingbloodglucose
FFA	Freefattyacids
GADA	Glutamicaciddecarboxylaseantibodies
GDM	Gestationaldiabetesmellitus
GFAP	Gliafibrillaryacidicprotein
GIP	Glucose-dependentinsulintropicpeptide
GLAST	L-glutamate/L-aspartatetransporter
GLP-1	Glucagon-likepeptide-1
GPX4	Glutathioneperoxidase4
GRP78	Glucose-regulatedprotein78
GRP78/Bip	Glucose-regulatedprotein78/ bindingimmunoglobulin protein
GS	Glutaminesynthase
GSH-PX	Glutathioneperoxidas
GSK3β	Glycogensynthasekinase3beta
HDL-C	High-densitylipoproteincholesterol
HFD	High-fatdiet
HOMA	Homeostasismodelassessment
HUVECs	Humanumbilicalveinendothelialcells

TABLE1(Continued)Listofabbreviationsandthecorrespondingfull terms.

IAA	Insulinantibodies
IBA-1	Ionizedcalciumbindingadaptormolecule1
ICA	Isletcellantibodies
ICAM-1	Intercellularadhesionmolecule1
ICV	Intracerebroventricular
IKK	IkBkinase
IL	Interleukin
iNOS	Induciblenitricoxidesynthase
IRE1α	Inositol-RequiringEnzyme1alpha
IRS-1	Insulinreceptorsubstrate-1
IkB	InhibitorofIkB
JAK	Januskinase
LD50	Lethaldose
LDL-C	Low-densitylipoproteincholesterol
MAPK	Mitogen-activatedproteinkinase
MCP-1	Monocytechemoattractantprotein-1(cc12)
MDA	Malondialdehyde
MMP-9	Matrixmetalloproteinase9
mTOR	Mechanistictargetofrapamycin

(Continuedinnextcolumn)

Abbreviation	Fullterms
MyD88	Myeloiddifferentiationprimaryresponse88
NADPH	Nicotinamideadeninedinucleotidephosphate
NF- κ B	Nuclearfactor κ 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 Integrations site for Moloney murine leukemia virus 2
PIPK	Phosphatidylinositol phosphate kinase
p-IRF3	Phosphorylated Interferon Regulatory Factor 3
PKC β 1	Protein kinase C beta 1
Pmpca	Peptidase mitochondrial processing alpha
PPAR	Peroxisome proliferator-activated receptor
Prx3	Peroxisome oxidin 3
p-SGK1	Phosphorylated Serum/Gluocorticoid 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	Shensongyangxin capsule
STAT	Signal transducer and activator of transcription
STZ	Streptozotocin
Sumo	Small Ubiquitin-like Modifier
SYT	Sanyetabiet
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAOC	Total antioxidant capacity
TC	Total cholesterol
TG	Triglycerides
TGF- β 1	Transforming growth factor- β 1

(Continued on following page)

TABLE1(Continued)Listofabbreviationsandthecorrespondingfull terms.

Abbreviation	Fullterms
TLR2/4	Toll-likereceptor2/4
TNF- α	Tumornecrosisfactor- α
TRIF	TIR-domain-containingadapter-inducinginterferon- β
TRPV1	Transientreceptorpotentialvanilloid1
Trx2	Thioredoxin

TrxR2	Thioredoxinreductase2
TXNIP	Thioredoxin-interactingprotein
VEGF2	Vascularendothelialgrowthfactorreceptor2
XBP-1	X-boxBindingProtein1
α 2-AR	Alpha-2adrenergicreceptor
γ GCS	Gamma-GlutamylcysteineSynthetase

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 the 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 (Zhanget 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

2.1.1 Insufficient insulin secretion

blood sugar levels.

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).

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 Type 1 diabetes (T1D), inadequate insulin secretion results in hepatic gluconeogenesis including phosphofructokinase and

primarily from autoimmune-mediated damage and death of insulin-secreting cells (Beck et al., 2019). This chronic autoimmune disease occurs when the immune system 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 occurs as the immune system misidentifies β -cells as foreign and destroys them.

phosphoenolpyruvate carboxykinase (PEPCK), decreasing glucose production from non-carbohydrate sources (Zhengetal., 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 the pancreas lead to inadequate insulin secretion and ultimately non-carbohydrate substrates, enhanced glycogen breakdown

hyperglycemia (Skylar, 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. Overtime, a progressive decline in pancreatic β -cell function may

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 inadequate insulin secretion. multiple microvascular complications, including diabeti

nephropathy and diabetic retinopathy. 2.1.2 Insulin resistance

Insulin resistance is a primary pathogenic mechanism in T2D

and a significant factor contributing to inadequate insulin insulin, leading to secretion. It denotes a diminished responsiveness of cells to impaired insulin biological activity (Gerich, 2003). To maintain

2.3 Abnormal intestinal hormones

Intestinal hormones, including glucagon, insulin, glucagon-like normal blood glucose levels, increased insulin secretion is required. dependent insulinotropic

peptide-1 (GLP-1), and

glucose-

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).

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,



FIGURE1
 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. energy metabolism, further exacerbating obesity and insulin resistance. Additionally, GLP-1 supports pancreatic β -cell function by promoting cell proliferation, differentiation, and survival, thereby preserving insulin production capacity. 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 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,

[etal., 2022](#)).
Additionally,

further disrupting hormonal balance ([Wong 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, it

s ability to enhance insulin secretion is significantly diminished due to reduced β -cell responsiveness. As a result, GIP fails to effectively

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 regulate blood glucose, further contributing to metabolic targeting of GLP-1 and GIP pathways, such as GLP-1 receptor

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 (Patlak 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

agonists and dipeptidylpeptidase-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

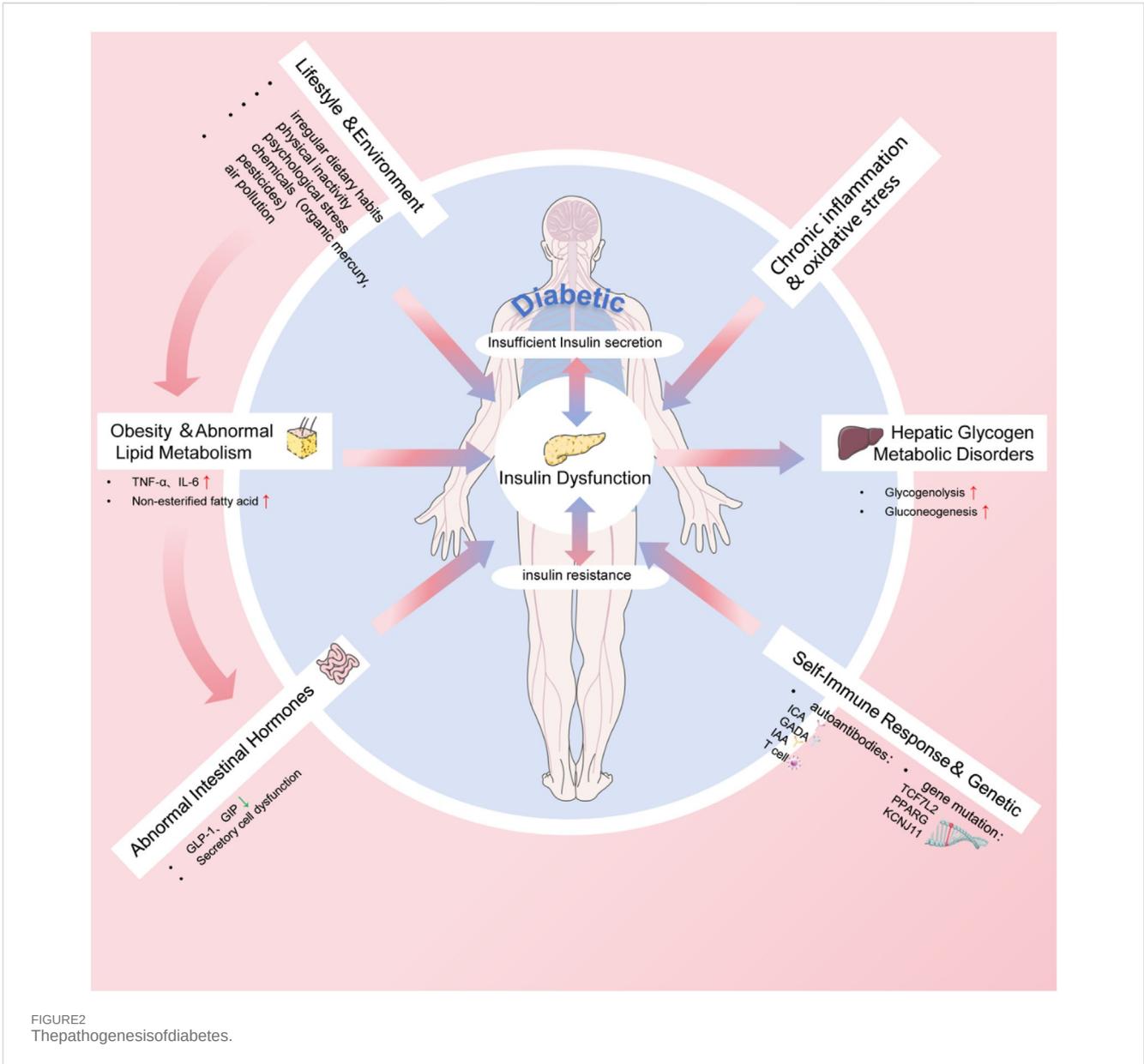


FIGURE2
The pathogenesis of diabetes.

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

cholesterol(HDL-C),andincreasedtriglycerides(TG).Theselipid abnormalitiesareriskfactorsforcardiovasculariseaseandcan further aggravate insulin resistance and the progression of diabetes (Fuetal.,2011).Withinadiposetissue,theoveraccumulationof lipidstriggersinflammatoryresponsesinadipocytesandinterferes withtheinsulinsignalingpathway,exacerbatinginsulinresistance andenergyexpenditure;reducedleptinsecretioncanresultin (Songetal.,2023). increasedappetiteandexcessiveenergyintake.Ontheother hand,TNF- α andIL-6actaspro-inflammatoryfactorsthat thebody'sinsulinsignalingpathway,therebyexacerbatinginsulin resistanceandelevatingbloodglucoselevels. increaseinsulinresistance.Theirexcessivesecretioncanimpair

2.5 Chronic inflammation and oxidative stress

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

Chronic inflammation and oxidative stress are critical contributors to impaired insulin 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/ Celllines	Dose/ Concentration	Efficacy	Mechanisms	Ref
Diabetes	—	NOD mice	100mg/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 60mg/kg	Wistar rats	1mg/kg(i.v.)	Reduce blood sugar	—	Hsu et al. (1997)
	HFD, 12 weeks	C57BL/6J	6.19mg/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 50mg/kg, 5 days	C57BL/6J	100mg/kg(i.g.)	Alleviate macrophage infiltration	Anti-Inflammatory, iNOS↓, TNF-α↓, IL-1β↓, MCP-1↓, JAK2/STAT↓	Zhu et al. (2017)
	AGEs 200μg/mL, 24h	HBZY-1	50μM	Inhibit Mesangial cell autophagy	Reduce the number of autophagosomes, LC3II/LC3I↑, RAGE↓, Col-IV↓, p-mTOR↑	Chen et al. (2017)
	STZ 65mg/kg(iv)	SD rats	10mg/kg(p.o.)	—	Anti-Inflammatory, TGF-β↓, Col-IV↓, ICAM-1↓	Fu et al. (2009)
	STZ 50mg/kg, 5 days	C57BL/6J	100mg/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 50mg/kg, 5 days	C57BL/6J, TLR2-/- mice	100mg/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	60mg/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 40mM, 48h; STZ 50mg/kg, 5 days	MPC5; C57BL/6J	40μM; 200mg/kg(i.p.)	Inhibit apoptosis	Anti-Inflammatory, TNF-α↓, IL-1β↓, WT-1↑, SYNPO↑, p-MLK1↓, RIPK1/RIPK3↓	Wang et al. (2022b)
	Glucose 1g/L	HBZY-1	10 ⁻⁶ -10 ⁻³ M	—	Anti-oxidative stress, Anti-Inflammatory, IL-6↓, MCP-1↓	Zhang et al. (2016)
	Glucose 30mM, 48h	Mouse mesangial cells	200μM	—	Anti-oxidative stress, NADPH↓, ROS↓, TGF-β↓, fibronectin↓	Sun et al. (2015)
	Glucose 30mM, 48h	BMDMs	10 ⁻⁶ -10 ⁻⁴ M	—	Anti-Inflammatory, TLR2↓, iNOS↓, MyD88↓, p-IRAK1↓, Trif↓, NF-κB p65↓, p-IRF3↓, IRF3↓	Shao et al. (2016)
	Glucose 40mM, 48h; STZ 50mg/kg, 5 days	MPC5; C57BL/6J	80μM; 200mg/kg(i.p.)	Restore autophagy	VEGF2↓, caspase3↓, PI3K/AKT↓	Wang et al. (2022c)
DPN	STZ 150mg/kg	ddY mice	30mg/kg(p.o.)	Modulate spinal nociceptive transmission	Activate α2-adrenoceptors, Norepinephrine	Lee et al. (2011)
	Glucose 150mM, 48h	RSC96	100μM	Inhibit apoptosis	Anti-oxidative stress, Nrf2/ARE↑, ROS↓, MDA↓, GST↑, GPX↑, Bcl-2↑, Bax↓, Caspase-3↓	Yang et al. (2015)
	Glucose 150mM, 24h	RSC96	10μM	Restoration of mitochondrial function	Pmpca↑, Sumo1↑, Trx2↑, TrxR2↑, Prx3↑, ROS↓	Yang J. et al. (2022)
DPN	Glucose 150mM, 24h	SCline	100μM	Inhibit ER stress and DRGn apoptosis	JNK↓, CHOP↓, XBP1s↑, IRE1α↓, GRP78↓, Bcl-2↑, Bax↓, Caspase-12↓, Caspase-3↓	Zhu et al. (2021)
Diabetic wounds	HGMEM, 48h; STZ 35mg/kg	HaCaT; SD rats	100μM; 30mg/kg(i.g.)	Promote proliferation and migration, Inhibit apoptosis	Anti-oxidative stress, Nrf2 pathway↑, VEGF↑, TGF-β1↑	Sun et al. (2020)

(Continued on following page)

TABLE2(Continued)MechanismofPFIndiabetesandcomplications.

Disease	Model Methods	Animal/ Celllines	Dose/ Concentration	Efficacy	Mechanisms	Ref
	HGMEM,48h; STZ35mg/kg	HaCaT; SDrats	100µM; 30mg/kg(i.g.)	—	Anti-Inflammatory, IL-1β↓, IL-18↓, TNF-α↓,CXCR2↓,NF-κB↓,IκB↑,NLRP3↓, Caspase-1↓	Sunetal. (2021)
	STZ55mg/kg, 5days	C57BL6/J	500µM,hydrogel	Promoteproliferationand maturation;	Anti-Inflammatory,CD86↓,TNF-α↓,IL-1β↓,iNOS↓,CD206↑,IL-10↑,TGF-β↑, Arg-1↑,CD31↑,VEGF↑, α-SMA↑,Col-1↑	Yang et al. (2021)
	STZ60mg/kg	SDrats	20mg/mL,hydrogel	Promoteangiogenesis, collagen deposition;	Anti-Inflammatory,IL-10↑,TNF-α↓, CD31↑	Guoetal. (2022)
NAFLD	HFD,12weeks	C57BL/6J	100mg/kg(i.g.)	—	Anti-Inflammatory,Triglyceride↓, Cholesterol↓,AST↓,TNF-α↓	Zhou etal. (2019)
	HFD,10weeks	SDrats	20mg/kg(i.g.)	Regulatelipidmetabolism	Anti-oxidativestress,TG↓,TC↓,FFA↓, FBG,ALT↓,AST↓,SOD↑,MDA↓, CYP2E1↓,ROS↓,IRS/Akt/GSK3β	Maetal. (2017a)
DLI	Glucose 300mM,24h; —	AML12;db/db,db/mmice	16µM; 100mg/kg(i.g.)	Inhibitapoptosis	Anti-Inflammatory,Anti-oxidativestress, IL-1β↓,IL-18↓,TNF-α↓,F4/80↓,ROS↓, ASC↓,Caspase-1↓,TXNIP/NLRP↓	Wang etal. (2022d)
Diabetic myocardial ischemicinjury	STZ150mg/kg	C57BL/6, TRPV1-/- mice	140mg/kg(i.g.)	—	TRPV1/CaMK/CREB/CGRP↑	Hanetal. (2016)
	STZ30mg/kg	SDrats	90mg/kg(i.g.)	Inhibitapoptosis	Anti-oxidativestress,SOD↑,MDA↓, Bax↓,Bcl-2↑,Caspase-3↓	Lietal. (2021b)
DR	Glucose25mM, 6hours; STZ60mg/kg	BV2; CD-1mice	10µM; 40mg/kg(p.o.)	—	Anti-Inflammatory,SOCS3↑,MMP-9↓, IBA-1↓,IL-1β↓,TLR4/p38/NF-κB↓	Peietal. (2023)
	STZ50mg/kg	SDrats	20mg/kg(i.g.)	Reducebloodsugar,Gliacellsactivation	GAFP↓,GLAST↑,GS↑	ZhangT. etal. (2019)
	STZ50mg/kg	SDrats	4mg/kg(i.p.)	—	Anti-Inflammatory, GAFP↓, IL-6↓, IL-1↓, TNF-α↓,JAK2/STAT3↓	Zhan g etal. (2022)
Diabeticvascular disease	Glucose25mM, 24h; STZ30mg/kg	HUVECs; SDrats	100µM; 10mg/kg(i.g.)	Inhibitapoptosis	Anti-Inflammatory,TNF-α↓,PKCβ1↓	Wang etal. (2019)
	STZ35mg/kg	C57BL/6J	100mg/kg(i.g.)	—	Anti-oxidativestress,ALT↓,AST↓, AGES↓	Huang etal. (2022)
Cognitive dysfunction	STZ35mg/kg	SDrats	30mg/kg(i.g.)	Inhibittau hyperphosphorylatio	Anti-Inflammatory,IL-1β↓,TNF-α↓, SOCS2↓,IRS-1↑,Akt↑,GSK-3β↑	Sunetal. (2017)
	STZ3mg/kg, day1and3	C57BL/6	10mg/kg(i.p.)	Regulatemitochondrialand isletdysfunction	Anti-oxidativestress,p-PI3K↑,p-Akt↑, p-IRS-1↓	Wang etal. (2018)
Pancreaticβ-cells injury	STZ3mM,24h	INS-1	80µM	Inhibitapoptosis	Anti-oxidativestress,Caspase-3↓,Bax↓, Bcl-2↑,ROS↓,MDA↓,SOD↑,p-p38↓, p-TNK↓,MAPK↓	LiuC. etal. (2019)
Gestation al diabetes	STZ25mg/kg	Albinorats	30mg/kg(p.o.)	Reducebloodsugar	Akt/mTOR↓,p-4E-BP1↓,p-SGK1↓	Zhan g etal. (2022)
	STZ35mg/kg	SDrats	30mg/kg(i.g.)	Inhibitferroptosis	ROS↓, MDA↓, GSH↑, p-PI3K↑, Akt/Nrf2/ GPX4↑	Lianetal. (2023)

(Continuedonfollowingpage)

TABLE2(Continued)MechanismofPFIndiabetesandcomplications.

Disease	Model Methods	Animal/ Celllines	Dose/ Concentration	Efficacy	Mechanisms	Ref
Diabeticcataract	Glucose 30mM,24h	SRA01/04	10µM	—	InhibitEMTof lensepithelialcells,Anti-oxidativestress,E-cadherin↑, N-cadherin↓,Vimentin↓,Snail↓,SOD↑, GSH-Px↑,MDA↓,Bax↓,c-caspase9↓, cytochrome c↓,Bcl-2↑,SIRT1↑	Zeng et al. (2022)
Diabetic periodontitis	STZ50mg/kg	Wistarrats	100mg/kg(i.g.)	Reducebone loss,enhance bonequality	Anti-Inflammatory,IL-1β↓,IL-6↓, TNF-α↓	Kuzu et al. (2023)

TABLE3MechanismofPFExtractandcompoundinDiabetesandComplications.

Disease	Model methods	Animal/ Celllines	Dose/Dosing method/period	Efficacy	Mechanisms	Ref
Diabetes	HFD 20week	C57BL/6N	SYT400mg/kg(i.g.)	Suppressiverlipogenesis	Anti-Inflammatory,TNF-α↓,IL-4↓,IL-6↓	Yaometal. (2021)
	—	db/dbmice	PFEExt200mg/kg(i.g.)	Reducebloodsugar	—	Changetal. (2016)
	—	db/dbmice	EAF100mg/kg(i.g.)	Reducebloodsugar	Anti-Inflammatory,Anti-oxidative stress,SOD↑,Catalase↑, MDA↓,ROS↓	Zhangetal. (2023a)
DN	STZ65mg/kg	Wistarrats	TGP200mg/kg(p.o.)	—	Anti-Inflammatory,Anti-oxidative stress,Col-VI↓,ICAM-1↓,IL-1↓, TNF-α↓,NF-κBp65↓,3-NT↓, nephrinprotein↑,TGF-β1↓	Wueta. (2009)
	STZ30mg/kg	SDrats	MC-TG808mg/kg(i.g.)	AmeliorateERstress-relatedinflammation	Anti-Inflammatory,GRP78/ Bip↓, XBP-1(s)↓,MCP-1↓,ICAM-1↓, p-IRF3↓,NF-κBp-65↓	Cheneta. (2016)
	STZ65mg/kg	Wistarrats	TGP200mg/kg(p.o.)	—	Anti-Inflammatory,JAK/STAT3↓	Wangetal. (2012)
	STZ65mg/kg	Wistarrats	TGP200mg/kg(p.o.)	—	Anti-Inflammatory,α-SMA↓, E-cad↑,TLR2↓	Zhangetal. (2014)
DPN	STZ60mg/kg	SDrats	TLN21.8g/kg(i.g.)	Improveurological function	Anti-oxidativestress,TAOC↑, ROS↓, Nrf2↑, γGCS↑, Bcl2↑, Bax↓, CytoC↓	Jieta. (2016)
	STZ60mg/kg	SDrats	TGP5.6mg/kg(i.g.)	Restoremitochondria l function	Pmpca↑,Sumo1↑,Trx2↑,TrxR2↑, Prx3↑,ROS↓	YangX. etal.(2022)
Diabeticwounds	STZ35mg/kg	SDrats	3%PF-SA-gelatin,skin scaffolds	Promoteangiogenesis, collagen deposition	Anti-Inflammation,IL-1β↓, CD31↑	Yuetal. (2022)
DLI	—	H4IIE	PR-Et400mg/kg	Reducebloodsugar	PEPCK↓	Juaneta. (2010)
Diabetic myocardialfibrosis	STZ40mg/kg, 2days	Wistarrats	SSYX200mg/kg	Inhibitcardiacfibrosis	Anti-Fibrosis,TGF-β1↓,Col-I↓, Col-III↓,MMP-2↓,MMP-9↓,α-SMA↓,p-Smad2/3↓,Smad7↑	Sheneta. (2014)
Glycemic variability	Glucose25mM, 24h STZ30mg/kg	HUVECs;SD rats	PAE100µM PAE10mg/kg(i.g.)	Plateletactivation	Anti-oxidativestress,CD62p↓, ROS↓,GSH-px↑	Huangetal. (2020)

mediators. These factors activate signaling pathways such as c-Jun N-terminal kinase (JNK) and IκB 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 (Radmehretal.,2025).

Oxidative stress further exacerbates diabetes pathogenesis by generating excess ROS through glucose autooxidation and the formation of advanced glycation end products (AGEs) (Khalid

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 [etal., 2022](#)). Elevated ROS levels not only damage β -cells but also psychological stress. Also, oxidative stress kinases that interfere with insulin signaling, obesity and poor dietary habits stand as predominant risk factors for T2D. Notably, inflammation and oxidative stress reinforce each other, creating a self-perpetuating cycle where inflammation induces ROS production, and oxidative

the easy access and consumption of high-sugar, high-fat, and high-calorie foods. Prolonged irregular eating patterns result in fat stress amplifies inflammatory signaling. Emerging research has accumulated, consequently expediting the development of explored therapeutic strategies targeting these mechanisms, insulin resistance and the onset of T2D (Ladher et al., 2023). including peroxisome proliferator-activated receptor (PPAR) Furthermore, consistent physical exercise not only aids in weight modulator 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

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

management.
of insulin

2.6 Self-immune response and genetic factors

The self-immune response is the body's immune response to its

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, own tissues, including the autoimmune attack on pancreatic β -cells, which is the main pathogenic mechanism of T1D (Nakayasu et al.,

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,

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-

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

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.

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

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, PPAR γ , 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.

3.1 Diabetes

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.

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 Paeoniae Alba (RPA) can significantly reduce fasting blood glucose levels in db/db mice and bring them to levels similar to C57J/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. studies PF reduced the activity of nicotinamide- Research has found that PF can protect NOD mice from the effects of T1D by modulating the gut microbiota and inhibiting the

dinucleotidephosphateoxidase(NADPH),anddecreasedthe levelofROS,transforminggrowthfactor- β 1(TGF- β 1)and fibronectininhighglucoseculturedmesangialcells(Sunetal., 2015). Although the anti-inflammatory efficacy of PF has been well illustrated in several animal models, whether it could attenuate DN anddetailedmechanismsarestillobscure.Thecurrentstudy

Toll-like receptor 4 (TLR4)-myeloid differentiation primary suggestedthathighglucoseactivatesmacrophagesprimarily response protein 88/TIR-domain-containing adapter-inducing throughTLR2- dependentmechanismswhichaggravatedthe

interferon- β (MyD88/TRIF) pathway (Zhu et al., 2017). severityofrenalinflammationandeventuallycontributedtoDN. Additionally,anovelanti-diabeticmonomercombination(AMC) treatment of T2D and prediabetes. Research has found that hasbeenproventohavesignificanttherapeuticeffectsonhigh-fat SYT can improve lipid metabolism and insulin sensitivity by diet(HFD)-inducedType2diabeticmice,anditsmechanismof inhibiting liver lipid synthesis pathways, such as down- actionmayinvolve theregulationofbacterial-co-metabolism- regulating Sterol Regulatory inflammatoryresponses(Hanetal.,2020).SanyeTablet(SYT)is Element-BindingProtein1/Acetyl-CoACarboxylase(SREBP1/ apatentedprescriptiondrugrichinPFandwidelyusedforthe

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).

ACC) and Janus Kinase/Transducer and Activator of Transcription (JAK/STAT) signaling pathways, and by However, the mechanism of autophagy regulation exerted by PF is also completely different in different cell lines. In MCP5 cells,

modulating the JAK-STAT pathway through its effect 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 (Zhan 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.

Wangetal.demonstratedthatPFcanrestorepodocyteautophagy
FactorReceptor2(VEGFR2)-mediatedthePI3K/AKTpathwayto
directlybindtoitbymoleculardockingandsurfaceplasmon
PFtreatmentofDN(Wangetal.,2022b).

andinhibitapoptosisbytargetingVascularEndothelialGrowth
improveDNinjury.Inaddition,VEGFR2asatargetofPFcan
resonancedetection,whichprovidesanewtheoreticalbasisfor

3.3Diabeticperipheralneuropathy(DPN)

3.2DN Among diabetic patients, DPN is prevalent and is characterized

DNiskidneydamagecausedbydiabetesmellitusandisa
prevalentcomplicationindiabeticpatients(HuQ.etal.,2023).
Asdiabetesprogresses,theglomerularfiltrationratedecreases,
microalbuminuriaandproteinuriadevelop,andmayeventually
leadtochronicrenalfailure(Alicicetal.,2017).Alargenumber
of studies have confirmed that nephropathy mitigates the
effects

bysymptomssuchasneuralgia,sensoryabnormalities,andmotor
PFbyinhibitingtheinflammatoryresponse,reducingoxidative
damageofmesangialcellsinducedbyAGEs,up-regulating
autophagyactivityandimmunomodulation(Figure3).These
cascadingeventsrequireco-regulationofthemultifariouscellular
of signaling pathways such as JAK2/STAT3 pathway, TLR2/4
pathway, Receptor for Advanced Glycation End
of products/mammalian target

disorders (Hammad et al., 2020; Jensen et al., 2021; Wan 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 of rapamycin signaling (RAGE/mTOR) pathway, enhances nervous system function in diabetic rats by modulating the Phosphatidylinositol 3-kinase/Protein Kinase B (PI3K/AKT) expression of mitochondrial thioredoxin (Trx2). Research has pathway, Plant Inositol Phosphate Kinase (PIPK1/PIPK3) shown that PF upregulates Trx2 expression and its associated pathway, Silent information regulator of transcription 1/Nuclear proteins, diminishes mitochondrial oxidative stress, and 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.,

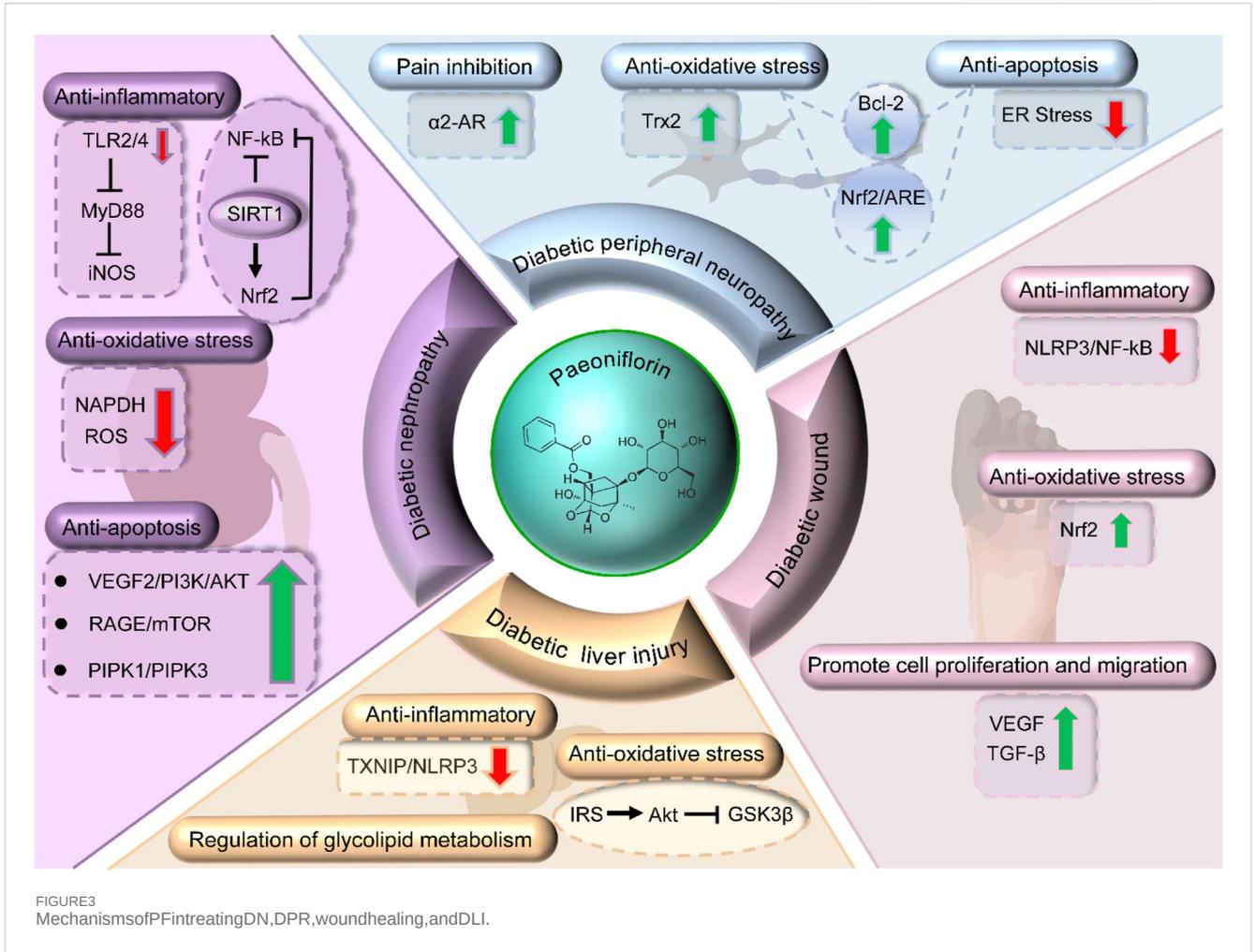
consequently mitigates nervous system damage in DPN patients (Yang Y. et al., 2022). Furthermore, PF mitigates nerve cell apoptosis by regulating the endoplasmic reticulum stress

2012; Zhang et al., 2014; Chen et al., 2016; Sun et al., 2017; 2017; Zhanget al., 2017; Shao et al., 2019; Wang et al., 2022a).

The study showed that PF and oxypaeniflorawere able to attenuate AGEs-induced oxidative damage and inflammation in

mesangial cells, thereby improving DN (Zhang et al., 2013).
In vitro

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.

epithelialization, and promotion

of collagen deposition, thereby effectively fostering wound healing

3.4 Diabetic wound

has demonstrated efficacy in hemostasis, antibacterial activity, modulation of macrophage polarization, inflammation reduction, enhancement of angiogenesis and

([Yang et al., 2021](#); [Guo et al., 2022](#); [Yu et al., 2022](#)). These findings offer crucial experimental validation for the therapeutic potential of

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

3.5 Diabetic liver injury (DLI)

PF in managing DFU.

Individuals with diabetes commonly experience DLI, marked by hepatic steatosis, inflammation, and aberrant liver function (Rao et al., 2021; Wang et al., 2023c; Thoudam et al., 2023). DLI 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- β 1 (Sun et al., 2020). Furthermore, PF can suppress the

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 inflammatory response mediated by NLRP3 and NF- κ B, disease by inhibiting gluconeogenesis, modulating lipid

consequently mitigating DFU inflammation and facilitating the healing process (Sun et al., 2021). Recently, there has been a

the insulin signaling pathway, and suppressing inflammatory responses (Ma et al., 2017b; Li et al., 2018a; Shu et al., 2019; Zhan et al., 2022b; Wan 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

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 (Zhan 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

conduct clinical trials assessing its efficacy and safety in diabetic patients. to fluctuations in blood glucose, elevated oxidative stress, and platelet activation (Mohammed et al., 2015; Ye et al., 2016;

Liu C. et al., 2019; SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration, 2023). PF, with its anti-

3.6 Diabetic myocardial ischemic injury

apoptotic, anti-inflammatory, and anti-thrombotic properties offers substantial protection against cardiovascular and

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

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 cardiomyopathy by suppressing the TGF- β 1/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

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 cardiomyopathy by suppressing the TGF- β 1/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

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. (etal., 2021b).

3.7 Diabetic retinopathy (DR)

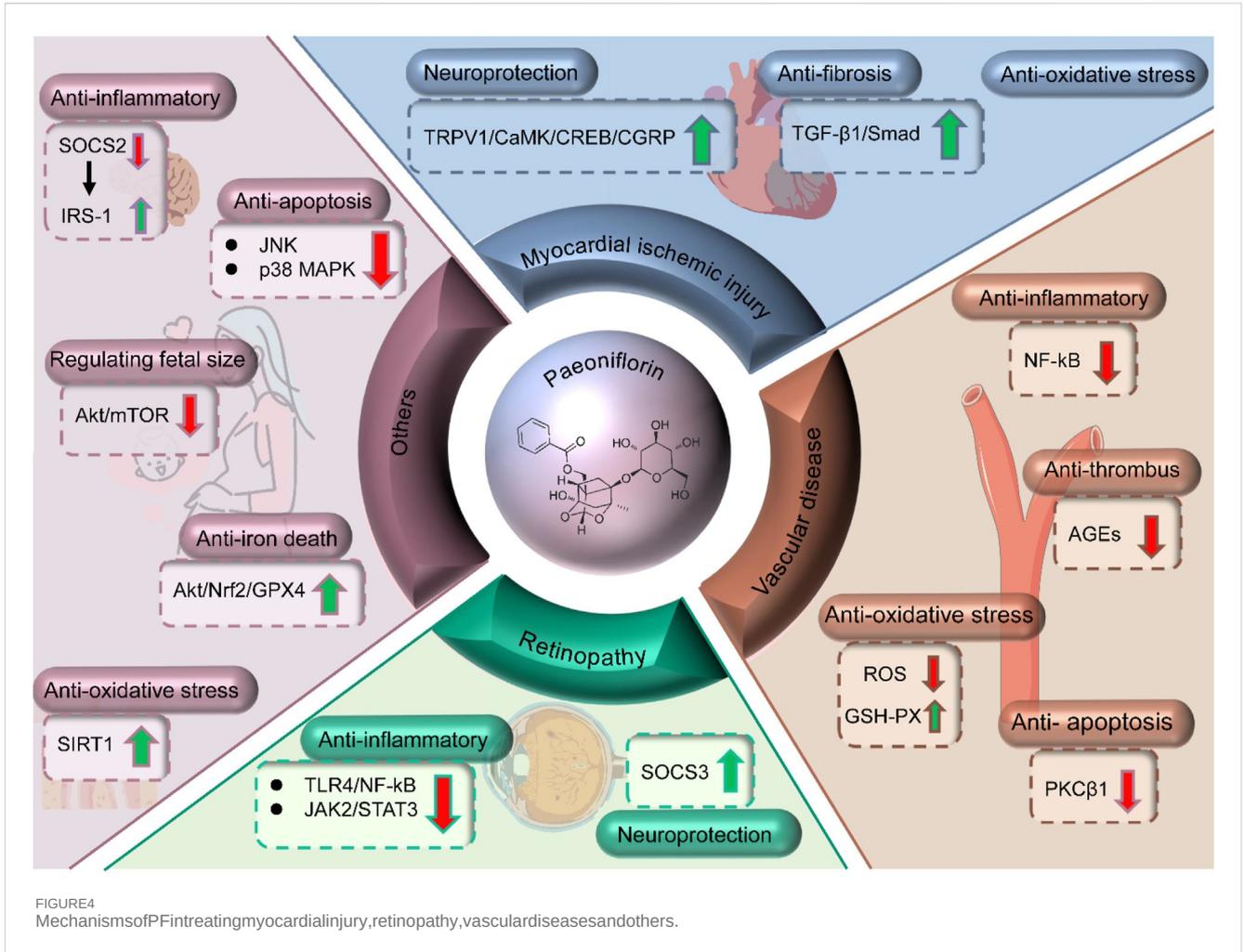
DR often leads to vision impairment (Yue et al., 2022; Bryl et al., 2022). Existing research indicates that inflammation of retinal microglial cells is instrumental in the progression of DR (Zhang Y. et al., 2019). Notably, matrix metalloproteinase 9 (MMP-9) in these cells critically compromises the integrity of the blood-retinal

3.9 Others

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.

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) (Zhan et al., 2020). PF treatment markedly ameliorates exposed to high glucose (Tu et al., 2019; Fan et al., 2020; Pei STZ- mitochondrial dysfunction, augments synapti

2023). A study suggested that PF could safeguard Müller cells in diabetic rat retinas by upregulating the expression of L-glutamate/



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 results indicate that PF may have potential therapeutic value in improving trabecular number and thickness.

managing diabetic periodontitis, particularly through its anti-inflammatory properties and role in preserving bone integrity. These findings suggest that PF might serve as a natural anti-diabetic agent by alleviating β -cell injury. In summary, as a natural monoterpene glycoside, PF presents a

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

complications. Nevertheless, despite the promising initial findings, further clinical investigations are imperative to validate its safety, efficacy, and elucidate its mechanisms of action.

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 P/CAF in pancreatic tissue of GDM rats, potentially via the Akt/Nrf2/

4 Pharmacokinetics of PF

GPX4 pathway to counter ferroptosis (Lian et al., 2023).

PF, a tetracyclic glycoside predominantly found in plants

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 (Zenget al., 2022). In a diabetic periodontitis model, PF demonstrated significant anti-inflammatory

Paeoniaceae 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 effect is by reducing pro-inflammatory cytokines, leading to metabolism of peony glycoside occurs in the liver through

decreased bone loss. Micro-CT analysis further revealed that PF treatment enhanced bone quality by increasing bone mineral density

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 *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 *et al.*, 2023). The distribution of PF to the target organs is essential for its pharmacologic action against diabetes. Additionally, PF

Genotoxicity and mutagenicity studies were conducted to assess the potential DNA-damaging effects of PF. The results of these studies indicate that 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).

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 (Wan 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, sodium-glucose cotransporter 2 (SGLT2) inhibitors. These drugs reduce hepatic glucose output and improve insulin sensitivity 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

Therefore, patients with impaired renal function may require dose adjustment to prevent drug accumulation and potential toxicity.

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.

sulfonylureas, GLP-1 receptor agonists, DPP-4 inhibitors, and regulate blood glucose through various mechanisms. Metformin (LaMoia and Shulman, 2021), sulfonylureas stimulate insulin agonists and DPP-4 inhibitors enhance incretin activity, and reabsorption (Xie et al., 2023). Despite their efficacy, long-term

discomfort, hypoglycemia, and unresolved safety concern

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,

necessitating the exploration of alternative therapies.

Natural compounds have gained increasing attention as 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 (Qi 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, suggesting a wide safety margin. Even at high oral doses, such as 3 g/kg, no significant adverse reactions or fatalities were observed in 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, major organs, including the liver and kidneys (Ngo et al., 2019). Prolonged use does not lead to significant toxicity or damage to However, further studies are necessary to explore potential long-

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 nanoemulsion, liposome, 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

Writing–reviewandediting.ZQ:Validation,Writing–reviewandediting.XZ:Fundingacquisition,Projectadministration, Supervision,Writing–reviewandediting.
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
Advance in omics technologies including proteomics, metabolomic and bioinformatics, can facilitate a deeper

Funding

understanding of PF's molecular mechanisms and identify novel therapeutic targets. Furthermore, Clustered Regularly Interspaced Short Palindromic Repeats - CRISPR-associated protein 9 (CRISPR-

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 (Grant No. KJQN202400133).

Despite its promising profile, the long-term safety of PF is 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.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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,

All claims expressed in this article are solely those of the author and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the

reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Alicic, R. Z., Rooney, M. T., and Tuttle, K. R. (2017). Diabetic kidney disease, challenges, progress, and possibilities. *Clin. J. Am. Soc. Nephrol.* 12(12), 2032–2045. doi:10.2215/CJN.11491116
- Armstrong, D. G., Boulton, A. J. M., and Bus, S. A. (2017). Diabetic foot ulcers and their recurrence. *N. Engl. J. Med.* 376(24), 2367–2375. doi:10.1056/NEJMra1615439
- Armstrong, D. G., Tan, T. W., Boulton, A. J. M., and Bus, S. A. (2023). Diabetic foot ulcers, A review. *JAMA* 330(1), 62–75. doi:10.1001/jama.2023.10578
- Bader, E., Migliorini, A., Gegg, M., Moruzzi, N., Gerdes, J., Roscioni, S. S., et al. (2016). Identification of proliferative and mature β -cells in the islets of Langerhans. *Nature* 535 (7612), 430–434. doi:10.1038/nature18624
- Bany Bakar, R., Reimann, F., and Gribble, F. M. (2023). The intestine as an endocrine organ and the role of gut hormones in metabolic regulation. *Nat. Rev. Gastroenterol. Hepatol.* 20(12), 784–796. doi:10.1038/s41575-023-00830-y
- Bayan, N., Yazdanpanah, N., and Rezaei, N. (2022). Role of toll-like receptor 4 in diabetic retinopathy. *Pharmacol. Res.* 175, 105960. doi:10.1016/j.phrs.2021.105960

Bonnefond, A., Boissel, M., Bolze, A., Durand, E., Toussaint, B., Vaillant, E., et al. (2020). Pathogenic variants in inactionable MODY genes are associated with type 2 diabetes. *Nat. Metab.* 2(10), 1126–1134. doi:10.1038/s42255-020-00294-3

Bossart, M., Wagner, M., Elvert, R., Evers, A., Hübschle, T., Kloeckener, T., et al. (2022). Effects on weight loss and glycaemic control with SAR441255, a potent unimolecular peptide GLP-1/GIP/GCGR agonist. *Cell Metab.* 34(1), 59–74. e10. doi:10.1016/j.cmet.2021.12.005

Bryl, A., Mrugacz, M., Falkowski, M., and Zorena, K. (2022). The effect of diet and lifestyle on the course of diabetic retinopathy—A review of the literature. *Nutrients* 14(6), 1252. doi:10.3390/nu14061252

Cai, T., Wang, X., Li, B., Xiong, F., Wu, H., and Yang, X. (2021). Deciphering the synergistic network regulation of active components from *SiNiSan* against irritable bowel syndrome via a comprehensive strategy. Combined effects of synephrine, paeoniflorin and naringin. *Phytomedicine* 86, 153527. doi:10.1016/j.phymed.2021.153527

Beck, R. W., Bergenstal, R. M., Laffel, L. M., and Pickup, J. C. (2019). Advances in technology for management of type 1 diabetes. *Lancet* 394(10205), 1265–1273. doi:10.1016/S0140-6736(19)31142-0

Beltramo, E., Mazzeo, A., and Porta, M. (2023). Release of pro-inflammatory/angiogenic factors by retinal microvascular cells is mediated by extracellular vesicles derived from M1-activated microglia. *Int. J. Mol. Sci.* 25(1), 15. doi:10.3390/ijms25010015

Bennet, H., Mollet, I. G., Balhuizen, A., Medina, A., Nagorny, C., Bagge, A., et al. (2016). Serotonin(5-HT) receptor 2b activation augments glucose-stimulated insulin

- Chen, J., Hou, X. F., Wang, G., Zhong, Q. X., Liu, Y., Qiu, H. H., et al. (2016). Terpene glycoside component from Moutan Cortex ameliorates diabetic nephropathy by regulating endoplasmic reticulum stress-related inflammatory responses. *J. Ethnopharmacol.* 193, 433–444. doi:10.1016/j.jep.2016.09.043
- Chen, J., Zhao, D., Zhu, M., Zhang, M., Hou, X., Ding, W., et al. (2017). Paeoniflorin ameliorates AGES-induced mesangial cell injury through inhibiting RAGE/mTOR/autophagy pathway. *Biomed. Pharmacother.* 89, 1362–1369. doi:10.1016/j.biopha.2017.03.016
- Hsu, F. L., Lai, C. W., and Cheng, J. T. (1997). Antihyperglycemic effects of paeoniflorin and 8-debenzoylpaeoniflorin, glucosides from the root of *Paeonia lactiflora*. *Planta Medica* 63(4), 323–325. doi:10.1055/s-2006-957692
- Chen, R., Shen, C., Xu, Q., Liu, Y., Li, B., Huang, C., et al. (2021). The permeability characteristics and interaction of main components from Si-Ni-Sanina MDCK epithelial cell monolayer model. *Xenobiotica* 51(2), 239–248. doi:10.1080/00498254.2017.1359433

- Hu, J., Ding, J., Li, X., Li, J., Zheng, T., Xie, L., et al. (2023). Distinct signatures of gut microbiota and metabolites in different types of diabetes, a population-based cross-sectional study. *EClinicalMedicine* 62, 102132. doi:10.1016/j.eclinm.2023.102132
- Hu, P. Y., Liu, D., Zheng, Q., Wu, Q., Tang, Y., and Yang, M. (2016). Elucidation of transport mechanism of paeoni florin and the influence of ligustilide, senkyunolide and senkyunolide on paeoni florin transport through mdck-mdr1 cells as blood-brain barrier in vitro model. *Molecules* 21(3), 300. doi:10.3390/molecules21030300
- Hu, Q., Jiang, L., Yan, Q., Zeng, J., Ma, X., and Zhao, Y. (2023). A natural products solution to diabetic nephropathy therapy. *Pharmacol. Ther.* 241, 108314. doi:10.1016/j.pharmthera.2022.108314
- Cole, J. B., and Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nat. Rev. Nephrol.* 16(7), 377–390. doi:10.1038/s41581-020-0278-5
- TRPV1 and TRPA1 in diabetes mellitus and obesity. *Semin. Immunopathol.* 38(3), 397–406. doi:10.1007/s12016-016-9377-3
- Derbenev, A. V., and Zsombok, A. (2016). Potential therapeutic value of TRPV1 and TRPA1 in diabetes mellitus and obesity. *Semin. Immunopathol.* 38(3), 397–406. doi:10.1007/s12016-016-9377-3

Fan, Q., Guan, X., Hou, Y., Liu, Y., Wei, W., Cai, X., et al. (2020). Paeoniflorin modulates gut microbial production of indole-3-lactate and epithelial autophagy to alleviate colitis in mice. *Phytomedicine* 79, 153345. doi:10.1016/j.phymed.2020.153345

Fu, J., Li, Y., Wang, L., Gao, B., Zhang, N., and Ji, Q. (2009). Paeoniflorin prevents diabetic nephropathy in rats. *Comp. Med.* 59(6), 557–566.

Fu, S., Yang, L., Li, P., Hofmann, O., Dicker, L., Hide, W., et al. (2011). Aberrant lipid metabolism disrupts calcium homeostasis causing liver

endoplasmic reticulum stress in obesity. *Nature* 473(7348), 528–531. doi:10.1038/nature09968

Gan, L., Xie, D., Liu, J., Bond Lau, W., Christopher, T. A., Lopez, B., et al. (2020). Small extracellular microvesicles mediated pathological communications between dysfunctional adipocytes and cardiomyocytes as a novel mechanism exacerbating ischemia/reperfusion injury in diabetic mice. *Circulation* 141(12), 968–983. doi:10.

nanoparticle-induced reduction in reproductive capacity and increase in germline apoptosis through suppressing DNA damage checkpoints in *Caenorhabditis elegans*. *Sci. Total Environ.* 871, 162189. doi:10.1016/j.scitotenv.2023.162189

Huang, F. W., Wu, W. Q., He, Y. Y., and Chen, J. W. (2022). Effect of paeoniflorin on diabetic macroangiopathy mice. *Lingnan J. Emerg. Med.* 27 (02), 105–107+111. doi:10.3969/j.issn.1671-301X.2022.02.002

Huang, Y., Wang, J. S., Yang, L., Yue, L., Zhang, L., Zhang, Y. H., et al. (2020). Paeoniflorin ameliorates glycaemic variability-induced oxidative stress and platelet activation in HUVECs and DM rats. *RSC Adv.* 10(69), 42605–42612. doi:10.1039/d0ra02036b

Ilonen, J., Lempainen, J., and Veijola, R. (2019). The heterogeneous pathogenesis of type 1 diabetes mellitus. *Nat. Rev. Endocrinol.* 15(11), 635–650. doi:10.1038/s41574-019-0254-y

Gerich, J. E. (2003). Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes mellitus. *Mayo Clin. Proc.* 78 (4), 447–456. doi:10.4065/78.4.447

Ghosh, A., Arora, B., Gupta, R., Anoop, S., and Misra, A. (2020). Effects of nationwide lockdown during COVID-19 epidemic on lifestyle and other medical issues of patients with type 2 diabetes in north India. *Diabetes Metab. Syndr.* 14 (5), 917–920. doi:10.1016/j.dsx.2020.05.044

Gorgogietas, V., Rajaei, B., Heeyoung, C., Santacreu, B. J., Marin-Cañas, S., Salpea, P., et al. (2023). GLP-1R agonists demonstrate potential to treat Wolfram syndrome in human preclinical models. *Diabetologia* 66(7), 1306–1321. doi:10.1007/s00125-023-05905-8

MCAO rats via endoplasmic reticulum stress- apoptotic signaling

pathway. *J. Ethnopharmacol.* 187, 313–324. doi:10.1016/j.jep.2016.04.024

Guardado Mendoza, R., Perego, C., Finzi, G., La Rosa, S., Capella, C., Jimenez-Ceja, L. M., et al.

Jansson Sigfrids, F., Dahlström, E. H., Forsblom, C., Sandholm, N., Harjutsalo, V., Taskinen, M. R., et al. (2021). Remnant cholesterol predicts progression of diabetic nephropathy and retinopathy in type 1 diabetes. *J. Intern. Med.* 290 (3), 632–645. doi:10.1111/joim.13298

Jensen, T. S., Karlsson, P., Gylfadottir, S. S., Andersen, S. T., Bennett, D. L., Tankisi, H., et al. (2021). Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management. *Brain* 144(6), 1632–1645. doi:10.1093/brain/awab070

Paeoniflorin suppresses TGF- β mediated epithelial- transition in pulmonary fibrosis through a Smad-dependent pathway. *Acta Pharmacol. Sin.* 37 (6), 794–804. doi:10.1038/aps.2016.36

Juan, Y. C., Tsai, W. J., Lin, Y. L., Wang, G. J., Cheng, J. J., Yang, H. Y., et al. (2010). The novel anti-

(2015). Delta cell death in the islet of Langerhans and the progression from normal glucose tolerance to type 2 diabetes in non-human primates (baboon, *Papio hamadryas*). *Diabetologia* 58(8), 1814–1826. doi:10.1007/s00125-015-3625-5

- Kalogeropoulou, D., Lafave, L., Schweim, K., Gannon, M. C., and Nuttall, F. Q. (2008). Leucine, when ingested with glucose, synergistically stimulates insulin secretion and lowers blood glucose. *Metabolism* 57(12), 1747–1752. doi:10.1016/j.metabol.2008.09.001
- Guo, C., Wu, Y., Li, W., Wang, Y., and Kong, Q. (2022). Development of a microenvironment-responsive hydrogel promoting chronically infected diabetic wound healing through sequential hemostatic, antibacterial, and angiogenic activities. *ACS Appl. Mater. Interfaces* 14(27), 30480–30492. doi:10.1021/acsami.2c02725
- Khalid, M., Petroianu, G., and Adem, A. (2022). Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. *Biomolecules* 12(4), 542. doi:10.3390/biom12040542

- Hædersdal, S., Lund, A., Nielsen-Hannerup, E., Maagensen, H., Forman, J. L., Holst, J. J., et al. (2022). The glucagon receptor antagonist LY2409021 does not affect gastrointestinal-mediated glucose disposal or the incretin effect in individuals with and without type 2 diabetes. *Eur. J. Endocrinol.* 187 (4), 507–518. doi:10.1530/EJE-22-0291
- Hammad, M. A., Syed Sulaiman, S. A., Alghamdi, S., Mangi, A. A., Aziz, N. A., and Mohamed Noor, D. A. (2020). Statin-related peripheral neuropathy among diabetic patients. *Diabetes Metab. Syndr.* 14(4), 341–346. doi:10.1016/j.dsx.2020.04.005
- Han, F., Zhou, D., Yin, X., Sun, Z., Han, J., Ye, L., et al. (2016). Paeoniflorin protects diabetic mice against myocardial ischemic injury via the transient receptor potential vanilloid 1/calcitonin gene-related peptide pathway. *Cell Biosci.* 6, 37. doi:10.1186/s13578-016-0085-7
- Han, L., Zhao, L. H., Zhang, M. L., Li, H. T., Gao, Z. Z., Zheng, X. J., et al. (2020). A novel anti-diabetic monomer combination alleviates insulin resistance through bacteria-cometabolism-inflammation responses. *Front. Microbiol.* 11, 173. doi:10.3389/fmicb.2020.00173
- Hermans, M. P., Bouenizabila, E., Daniel Amoussou-Guenou, K., Jules Gninkoun, C., Ahn, S. A., and Rousseau, M. F. (2022). Fatty liver and atherogenic dyslipidemia have opposite effects on diabetic micro- and macrovascular disease. *Diabetes Metab. Syndr.* 16(10), 102613. doi:10.1016/j.dsx.2022.102613
- Hoofnagle, J. H., and Björnsson, E. S. (2019). Drug-induced liver injury - types and

- Friedman, J.E., et al. (2002). TNF- α is a predictor of insulin resistance in human pregnancy. *Diabetes* 51(7), 2207–2213. doi:10.2337/diabetes.51.7.2207
- Krause, M., and DeVito, G. (2023). Type 1 and type 2 diabetes mellitus, commonalities, differences and the importance of exercise and nutrition. *Nutrients* 15(19), 4279. doi:10.3390/nu15194279
- Kuzu, T. E., Öztürk, K., Gürkan, C. A., Yay, A., Göktepe, Ö., and Kantarcı, A. (2023). Anti-inflammatory and pro-regenerative effects of a monoterpeneglycoside on experimental periodontitis in a rat model of diabetes. *J. Periodontol.* 58(5), 932–938. doi:10.1111/jre.13151
- Ladher, N., Hinton, R., and Veitch, E. (2023). Challenges of obesity and type 2 diabetes require more attention to food environment. *BMJ* 383:2269. doi:10.1136/bmj.p2269
- LaMoia, T.E., and Shulman, G.I. (2021). Cellular and molecular mechanisms of metformin action. *Endocr. Rev.* 42(1), 77–96. doi:10.1210/endo/bnaa023
- Lee, K.K., Omiya, Y., Yuzurihara, M., Kase, Y., and Kobayashi, H. (2011). Antinociceptive effect of paeoniflorin in spinal α_2 -adrenoceptor activation in diabetic mice. *Eur. J. Pain* 15(10), 1035–1039. doi:10.1016/j.ejpain.2011.04.011
- Lei, Y., Gong, L., Tan, F., Liu, Y., Li, S., Shen, H., et al. (2019). Vaccarin ameliorates insulin resistance and steatosis by activating the AMPK signaling pathway. *Eur. J. Pharmacol.* 851, 13–24. doi:10.1016/j.ejphar.2019.02.029
- Levy, M., Prentice, M., and Wass, J. (2019). Diabetes insipidus. *BMJ* 364: l321. doi:10.1136/bmj.l321

- Li, L., Wang, H., Zhao, S., Zhao, Y., Chen, Y., Zhang, J., et al. (2022). Paeoniflorin ameliorates lipopolysaccharide-induced acute liver injury by inhibiting oxidative stress and inflammation via SIRT1/FOXO1a/SOD2 signaling in rats. *Phytother. Res.* 36(6), 2558–2571. doi:10.1002/ptr.7471
- Li, R., Andreu-Sánchez, S., Kuipers, F., and Fu, J. (2021a). Gut microbiome and bile

Malik, R. A. (2020). Diabetic neuropathy, A focus on small fibres. *Diabetes Metab. Res. Rev.* 36(Suppl.1),e3255.doi:10.1002/dmrr.3255

Mansour Aly, D., Dwivedi, O. P., Prasad, R. B., Käräjämäki, A., Hjort, R., Thangam, M.,etal.(2021).Genome-wideassociationanalyseshighlightetiologicaldifferences underlying newly defined subtypes of diabetes. *Nat. Genet.* 53 (11), 1534–1542. doi:10.1038/s41588-021-00948-2

101493.doi:10.1016/j.beem.2021.101493

(2021b). Study on

Li, S. S., Tian, C. Y., Zhang, G. W., Ma, L. L., Li, J. A., Liu, J. X., et al.

improvementeffectsandmechanismofpaeoniflorinonmyocardialinjuryintype

McAlister, E., Kirkby, M., Domínguez-Robles, J., Paredes, A. J., Anjani, Q. K., Moffatt, K., et al. (2021). The role of microneedle arrays in drug delivery and patient monitoring to prevent diabetes-induced fibrosis. *Adv. Drug Deliv. Rev.* 175,113825.doi:10.1016/j.addr.2021.06.002

2 diabetic model rats. *China Pharm.* 32 (23), 2846–2853. doi:10.6039/j.issn.1001-0408. 2021.23.06

Mei, Y., Tong, X., Hu, Y., Liu, W., Wang, J., Lv, K., et al. (2023). Comparative

Li, X., Sun, C., Zhang, J., Hu, L., Yu, Z., Zhang, X., et al. (2023). Protective effects of paeoniflorin on cardiovascular diseases, A pharmacological and mechanistic overview. *Front. Pharmacol.* 14,1122969.doi:10.3389/fphar.2023.1122969

Li, Y., Liu, Y., Liu, S., Gao, M., Wang, W., Chen, K., et al. (2023). Diabetic vascular diseases, molecular mechanisms and therapeutic strategies. *Signal Transduct. Target Ther.* 8(1),152.doi:10.1038/s41392-023-01400-z

Li, Y. C., Qiao, J. Y., Wang, B. Y., Bai, M., Shen, J. D., and Cheng, Y. X. (2018b). Paeoniflorin ameliorates fructose-induced insulin resistance and hepatic steatosis by activating LKB1/AMPK and AKT pathways. *Nutrients* 10(8),1024.doi:10.3390/nu10081024

Li, Z., Liu, J., Zhang, D., Du, X., Han, L., Lv, C., et al. (2018a). Nuciferine and paeoniflorin can be quality markers of Tangzhiqing tablet, a Chinese traditional patent medicine, based on the qualitative, quantitative and dose-exposure-response analysis. *Phytomedicine* 44,155–163.doi:10.1016/j.phymed.2018.02.006

Lian, L. B., Chen, B., and Duan, B. (2023). Influence of paeoniflorin on ferroptosis in rats with gestational diabetes mellitus by regulating Akt/Nrf2/GPX4 pathway. *Chin.*

J. Birth Health Hered. 31(01),22–26.doi:10.13404/j.cnki.cjbhh.2023.01.001

Liang, D., Liu, L., Qi, Y., Nan, F., Huang, J., Tang, S., et al. (2024). Jin-Gui-Shen-Qi

Wan alleviates fibrosis in mouse diabetic nephropathy via MHC class II. *J. Ethnopharmacol.* 324,117745.doi:10.1016/j.jep.2024.117745

Ling, Q., Xu, X., Wang, B. H., Li, L. J., and Zheng, S. (2016). The origin of new-onset diabetes after liver transplantation, liver, islets, or gut? *Transplantation* 100(4), 808–813.doi:10.1097/TP.0000000000001111

Liu, C., Ge, H. M., Liu, B. H., Dong, R., Shan, K., Chen, X., et al. (2019). Targeting pericyte-endothelial cell crosstalk by circular RNA-cPWWP2A inhibition aggravates diabetes-induced microvascular dysfunction. *Proc. Natl. Acad. Sci. U.S.A.* 116(15), 7455–7464.doi:10.1073/pnas.1814874116

Liu, J. L., Zhang, L., Huang, Y., Li, X. H., Liu, Y. F., Zhang, S. M., et al. (2023a). Epsin1-mediated exosomal sorting of DII4 modulates the tubular-macrophage crosstalk in diabetic nephropathy. *Mol. Ther.* 31(5),1451–1467.doi:10.1016/j.ymthe.2023.03.027

pharmacokinetics of six bioactive components of Shen-Wu-Yi-Shen tablets in normal and chronic renal failure rats based on UPLC-MS/MS. *J. Ethnopharmacol.* 317, 116818. doi:10.1016/j.jep.2023.116818

Mohammedi, K., Bellili-Muñoz, N., Marklund, S. L., Driss, F., Le Nagard, H., Patente, T.A., et al. (2015). Plasma extracellular superoxide dismutase concentration, allelic variations in the SOD3 gene and risk of myocardial infarction and all-cause mortality in people with type 1 and type 2 diabetes. *Cardiovasc Diabetol.* 14, 845. doi:10.1186/s12933-014-0163-2

Nakayasu, E. S., Bramer, L. M., Ansong, C., Schepmoes, A. A., Fillmore, T. L., Gritsenko, M. A., et al. (2023). Plasma protein biomarkers predict the development of persistent autoantibodies and type 1 diabetes 6 months prior to the onset of autoimmunity. *Cell Rep. Med.* 4(7), 101093. doi:10.1016/j.xcrm.2023.101093

Natale, P., Green, S. C., Tunnicliffe, D. J., Pellegrino, G., Toyama, T., and Strippoli, G. F. (2025). Glucagon-like peptide 1 (GLP-1) receptor agonists for people with chronic kidney disease and diabetes. *Cochrane database Syst. Rev.* 2(2), CD015849. doi:10.1002/14651858.CD015849.pub2

Newman, C. B., Preiss, D., Tobert, J. A., Jacobson, T. A., Page, R. L. 2nd, Goldstein, L. B., et al. (2019). Statin safety and associated adverse events, A scientific statement from the American heart association. *Arterioscler. Thromb. Vasc. Biol.* 39(2), e38–e81. doi:10.1161/ATV.0000000000000073

Ngo, T., Kim, K., Bian, Y., Noh, H., Lim, K. M., Chung, J. H., et al. (2019). Antithrombotic effects of paeoniflorin from paeonia suffruticosa by selective inhibition on shear stress-induced platelet aggregation. *Int. J. Mol. Sci.* 20(20), 5040. doi:10.3390/ijms20205040

Oikonomou, E. K., and Antoniadou, C. (2019). The role of adipose tissue in cardiovascular health and disease. *Nat. Rev. Cardiol.* 16(2), 83–99. doi:10.1038/s41569-018-0097-6

Pan, L., Cho, K. S., Yi, L., To, C. H., Chen, D. F., and Do, C. W. (2021). Baicalein, baicalin, and wogonin: protective effects against ischemia-induced neurodegeneration in the brain and retina. *Oxidative Med. Cell. Longev.* 2021, 8377362. doi:10.1155/2021/8377362

Liu, T., Zhuang, Z., and Wang, D. (2023b). Paeoniflorin mitigates high glucose-induced lifespan reduction by inhibiting insulin signaling in *Caenorhabditis elegans*. *Front. Pharmacol.* 14, 1202379. doi:10.3389/fphar.2023.1202379

Liu, Y., Han, J., Zhou, Z., and Li, D. (2019). Paeoniflorin protects pancreatic β cells

Pathak, P., Xie, C., Nichols, R. G., Ferrell, J. M., Boehme, S., Krausz, K. W., et al. (2018). Intestine farnesoid X receptor agonist and the gut microbiota activate G-protein bile acid receptor-1 signaling to improve metabolism. *Hepatology* 68(4), 1574–1588. doi:10.1002/hep.29857

from STZ-induced damage through inhibition of the p38 MAPK and JNK signaling pathways. *Eur. J. Pharmacol.* 853, 18–24. doi:10.1016/j.ejphar.2019.03.025

Liu, Z. Q., Jiang, Z. H., Liu, L., and Hu, M. (2006). Mechanisms responsible for poor oral bioavailability of paeoniflorin, Role of intestinal disposition and interactions with

Pei, X., Tang, S., Jiang, H., Zhang, W., Xu, G., Zuo, Z., et al. (2023). Paeoniflorin liver axis and reversal of pyroptosis. *Sci. Total Environ.* 904, 166885. doi:10.1016/j.scitotenv.2023.166885

Long, M. T., Noureddin, M., and Lim, J. K. (2022). AGA clinical practice update, diagnosis and management of nonalcoholic fatty liver disease in lean individuals, expert review. *Gastroenterology* 163(3), 764–774. e1. doi:10.1053/j.gastro.2022.06.023

recued hepatotoxicity under zinc oxide nanoparticle exposure via regulation on gut-
scitotenv.2023.166885

Luo, C., Yang, D., Hou, C., Tan, T., and Chao, C. (2023). Paeoniflorin protects NOD mice from T1D through regulating gut microbiota and TLR4 mediated MyD88/TRIF pathway. *Exp. Cell Res.* 422(1), 113429. doi:10.1016/j.yexcr.2022.113429

Qin,S.,Tang,H.,Li,W.,Gong,Y.,Li,S.,Huang,J.,etal.(2020).AMPKandits activator berberine in the treatment of neurodegenerative diseases. *Curr. Pharm. Des.* 26 (39),5054–5066.doi:10.2174/1381612826666200523172334

Qiu,Y.,Gan,M.,Wang,X.,Liao,T.,Chen,Q.,Lei,Y.,etal.(2023).Theglobal perspectiveonperoxisomeproliferator-activatedreceptorγ(PPARγ)inectopicfat deposition: a review. *Int. J. Biol. Macromol.* 253 (Pt 5), 127042. doi:10.1016/j.ijbiomac.

Luo,W.,Deng,J.,He,J.,Yin,L.,You,R.,Zhang,L.,etal.(2023).Integrationof 2023.127042

moleculardocking,moleculardynamicsandnetworkpharmacologytoexplorethe multi-targetpharmacologyoffenugreekagainstdiabetes.*J.Cell.Mol.Med.*27(14), 1959–1974.doi:10.1111/jcmm.17787

Radmehr, E., Yazdanpanah, N., and Rezaei, N. (2025). Non-coding RNAs affecting NLRP3 inflammasome pathway in diabetic cardiomyopathy: a comprehensive review of potential therapeutic options. *J. Transl. Med.* 23(1), 249. doi:10.1186/s12967-025-06269-w

sulfonylureas and glinides. *Curr. Top. Med. Chem.* 20(1), 37–56. doi:10.2174/1568026620666191224141617

Ma, M., Di, H. J., Zhang, H., Yao, J. H., Dong, J., Yan, G. J., et al. (2017c). Development of phospholipid vesicle-based permeation assay models capable of evaluating percutaneous penetration enhancing effect. *Drug Dev. Ind. Pharm.* 43(12), 2055–2063. doi:10.1080/03639045.2017.1371730

Ma, Z., Chu, L., Liu, H., Wang, W., Li, J., Yao, W., et al. (2017a). Beneficial effects of paeoniflorin on non-alcoholic fatty liver disease induced by high-fat diet in rats. *Sci. Rep.*

7, 44819. doi:10.1038/srep44819

Ma, Z., Liu, H., Wang, W., Guan, S., Yi, J., and Chu, L. (2017b). Paeoniflorin suppresses lipid accumulation and alleviates insulin resistance by regulating the Rho kinase/IRS-1 pathway in palmitate-induced HepG2 Cells. *Biomed. Pharmacother.* 90, 361–367. doi:10.1016/j.biopha.2017.03.087

MacDonald, P. E., and Rorsman, P. (2023). Metabolic messengers, glucagon. *Nat. Metab.* 5(2), 186–192. doi:10.1038/s42255-022-00725-3

Rao, Y., Kuang, Z., Li, C., Guo, S., Xu, Y., Zhao, D., et al. (2021). Gut Akkermansia muciniphila ameliorates metabolic dysfunction-associated fatty liver disease by regulating the metabolism of L-aspartate via gut-liver axis. *Gut Microbes* 13(1), 1–19. doi:10.1080/19490976.2021.1927633

Reed, D., Kumar, D., Kumar, S., Raina, K., Punia, R., Kant, R., et al. (2021). Transcriptome and metabolome changes induced by bitter melon (*Momordica charantia*)-intake in a high-fat diet induced obesity model. *J. Tradit. Complement. Med.* 12(3), 287–301. doi:10.1016/j.jtcme.2021.08.011

Ren, S., Wang, Y., Zhang, Y., Yan, P., Xiao, D., Zhao, Y., et al. (2023). Paeoniflorin alleviates AngII-induced cardiomyocyte hypertrophy in H9c2 cells by regulating oxidative stress and Nrf2 signaling pathway. *Biomed. Pharmacother.* 165, 115253. doi:10.1016/j.biopha.2023.115253

Sandoval, D. A., and D'Alessio, D. A. (2015). Physiology of proglucagon peptides, role of glucagon and GLP-1 in health and disease. *Physiol. Rev.* 95 (2), 513–548. doi:10.1152/physrev.00013.2014

Sanghera, D. K., Demirci, F. Y., Been, L., Ortega, L., Ralhan, S., Wander, G. S., et al. (2022a). Paeoniflorin (2022a). Paeoniflorin (2010). PPAR γ and ADIPOQ gene polymorphisms increase type 2 diabetes mellitus risk in Asian Indian Sikhs, Pro12Ala still remains as the strongest predictor. *Metabolism* 59(4), 492–501. doi:10.1016/j.metabol.2009.07.043

Santoro, A., and Kahn, B. B. (2023). Adipocyte regulation of insulin sensitivity and the risk of type 2 diabetes. *N. Engl. J. Med.* 388(22), 2071–2085. doi:10.1056/NEJMr2216691

1150. doi:10.3109/00498254.2016.1149633

SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration (2023). SCORE2-Diabetes 10-year cardiovascular risk estimation in type 2 diabetes in Europe. *Eur. Heart J.* 44(28), 2544–2556. doi:10.1093/eurheartj/ehad260

Wang, A., Gong, Y., Pei, Z., Jiang, L., Xia, L., and Wu, Y. (2016). Paeoniflorin ameliorates diabetic liver injury by targeting the TXNIP-mediated NLRP3 inflammasome in db/db mice. *Int. Immunopharmacol.* 109, 108792. doi:10.1016/j.intimp.2022.108792

Wang, C., Yuan, J., Zhang, L. L., and Wei, W. (2016). Pharmacokinetic comparisons of Paeoniflorin and Paeoniflorin-6'-O-benzenesulfonate in rats via different routes of administration. *Xenobiotica* 46(12), 1142–1150. doi:10.3389/fphar.2019.01551

Shao, Y. X., Gong, Q., Qi, X. M., Wang, K., and Wu, Y. G. (2019). Paeoniflorin ameliorates macrophage infiltration and activation by inhibiting the TLR4 signaling pathway in diabetic nephropathy. *Front. Pharmacol.* 10, 566. doi:10.3389/fphar.2019.01551

- Wang, D., Liu, L., Li, S., and Wang, C. (2018). Effects of paeoniflorin on neurobehavior, oxidative stress, brain insulin signaling, and synaptic alterations in intracerebroventricular streptozotocin-induced cognitive impairment in mice. *Physiol. Behav.* 191, 12–20. doi:10.1016/j.physbeh.2018.03.016
- Wang, J. S., Huang, Y., Zhang, S., Yin, H. J., Zhang, L., Zhang, Y. H., et al. (2019). A protective role of paeoniflorin in fluctuant hyperglycemia-induced vascular endothelial injuries through antioxidative and anti-inflammatory effects and reduction of PKC β 1. *J. Ethnopharmacol.* 193, 377–386. doi:10.1016/j.jep.2016.00566
- Shao, Y. X., Xu, X. X., Li, Y. Y., Qi, X. M., Wang, K., Wu, Y. G., et al. (2016). Paeoniflorin inhibits high glucose-induced macrophage activation through TLR2-dependent signal pathways. *J. Ethnopharmacol.* 193, 377–386. doi:10.1016/j.jep.2016.00566

Oxid.Med.CellLongev.2019,5647219.doi:10.1155/2019/5647219

Wang,K.,Wu,Y.G.,Su,J.,Zhang,J.J.,Zhang,P.,andQi,X.M.(2012).Total glucosides of paeony regulates JAK2/STAT3 activation and macrophage proliferation in diabetic rat kidneys. Am. J. Chin. Med. 40 (3), 521–536. doi:10.1142/S0192415X12500401

08.035

Shao,Y.X.,Xu,X.X.,Wang,K.,Qi,X.M.,andWu,Y.G.(2017).Paeoniflorin

attenuates incipient diabetic nephropathy in streptozotocin-induced mice by the suppression of the Toll-like receptor-2 signaling pathway. Drug Des. Devel Ther. 11, 3221–3233. doi:10.2147/DDDT.S149504

Wang, M., Zhang, Q., Lou, S., Jin, L., Wu, G., Wu, W., et al. (2023a). Inhibition of nephropathy in mice. *Biomed. Pharmacother.* 168, 115660. doi:10.1016/j.biopha.2023.115660

Shen, N., Li, X., Zhou, T., Bilal, M. U., Du, N., Hu, Y., et al. (2014). Shensong

MD2 by natural product-driven JM-9 attenuates renal inflammation and diabetic

2023.115660

Capsule prevents diabetic myocardial fibrosis by inhibiting TGF- β 1/Smad signaling. *J. Ethnopharmacol.* 157, 161–170. doi:10.1016/j.jep.2014.09.035

Shu, J. L., Zhang, X. Z., Han, L., Zhang, F., Wu, Y. J., Tang, X. Y., et al. (2019). Paeoniflorin-6'-O-benzenesulfonate alleviates collagen-induced arthritis in mice by downregulating BAFF-TRAF2-NF- κ B signaling, comparison with biological agents. *Acta Pharmacol. Sin.* 40(6), 801–813. doi:10.1038/s41401-018-0169-5

Sims, E. K., Carr, A. L. J., Oram, R. A., DiMeglio, L. A., and Evans-Molina, C. (2021). 100 years of insulin, celebrating the past, present and future of diabetes therapy. *Nat. Med.* 27(7), 1154–1164. doi:10.1038/s41591-021-01418-2

Skyler, J. S. (2023). Importance of residual insulin secretion in type 1 diabetes. *Lancet Diabetes Endocrinol.* 11(7), 443–444. doi:10.1016/S2213-8587(23)00149-3

Song, S., Xiao, X., Guo, D., Mo, L., Bu, C., Ye, W., et al. (2017). Protective effects of Paeoniflorin against AOPP-induced oxidative injury in HUVECs by

blocking the ROS-HIF-1 α /VEGF pathway. *Phytomedicine* 34, 115–126. doi:10.1016/j.phymed.2017.08.010

Song, W., Postoak, J. L., Yang, G., Guo, X., Pua, H. H., Bader, J., et al. (2023). Lipid kinase PIK3C3 maintains healthy brown and white adipose tissues to prevent metabolic diseases. *Proc. Natl. Acad. Sci. U.S.A.* 120(1), e2214874120. doi:10.1073/pnas.2214874120

Sun, M., Huang, L., Zhu, J., Bu, W., Sun, J., and Fang, Z. (2015). Screening nephroprotective compounds from cortex Moutan by mesangial cell extraction and UPLC. *Arch. Pharm. Res.* 38(6), 1044–1053. doi:10.1007/s12272-014-0469-3

Sun, X., Li, S., Xu, L., Wang, H., Ma, Z., Fu, Q., et al. (2017). Paeoniflorin ameliorates cognitive dysfunction via regulating SOCS2/IRS-1 pathway in diabetic rats. *Physiol. Behav.* 174, 162–169. doi:10.1016/j.physbeh.2017.03.020

Sun, X., Wang, X., Zhao, Z., Chen, J., Li, C., and Zhao, G. (2020). Paeoniflorin accelerates foot wound healing in diabetic rats through activating the Nrf2 pathway. *Acta histochem.* 122(8), 151649. doi:10.1016/j.acthis.2020.151649

- Wang, T., Shan, M. Y., Tang, C. Y., Cheng, M. Y., Chen, B., Yan, J., et al. (2023b). Linarin ameliorates diabetic liver injury by alleviating oxidative stress and inflammation through the inhibition of AKR1B1. *Comb. Chem. High. Throughput Screen* 26. doi:10.2174/138620732666230412084201
- Wang, W., Ji, Q., Ran, X., Li, C., Kuang, H., Yu, X., et al. (2023c). Prevalence and risk factors of diabetic peripheral neuropathy, A population-based cross-sectional study in China. *Diabetes Metab. Res. Rev.* 39(8), e3702. doi:10.1002/dmrr.3702
- Wang, X., Jiang, L., Liu, X. Q., Huang, Y. B., Wang, A. L., Zeng, H. X., et al. (2022b). Paeoniflorin binds to VEGFR2 to restore autophagy and inhibit apoptosis for podocyte protection in diabetic kidney disease through PI3K-AKT signaling pathway. *Phytomedicine* 106, 154400. doi:10.1016/j.phymed.2022.154400
- Wang, X., Liu, X. Q., Jiang, L., Huang, Y. B., Zeng, H. X., Zhu, Q. J., et al. (2022c). Paeoniflorin indirectly binds to TNFR1 to regulate podocyte necroptosis in diabetic kidney disease. *Front. Pharmacol.* 13, 966645. doi:10.3389/fphar.2022.966645
- Wang, Y., You, K., You, Y., Li, Q., Feng, G., Ni, J., et al. (2022d). Paeoniflorin prevents aberrant proliferation and differentiation of intestinal stem cells by controlling C1q release from macrophages in chronic colitis. *Pharmacol. Res.* 182, 106309. doi:10.1016/j.phrs.2022.106309
- Wen, J., Xu, B., Sun, Y., Lian, M., Li, Y., Lin, Y., et al. (2019). Paeoniflorin protects against intestinal ischemia/reperfusion by activating LKB1/AMPK and promoting autophagy. *Pharmacol. Res.* 146, 104308. doi:10.1016/j.phrs.2019.104308
- Wong, C. K., Yusta, B., Koehler, J. A., Baggio, L. L., McLean, B. A., Matthews, D., et al. (2022). Divergent roles for the gut intraepithelial lymphocyte GLP-1R in control of metabolism, microbiota, and T cell-induced inflammation. *Cell Metab.* 34(10), 1514–1531.e7. doi:10.1016/j.cmet.2022.08.003
- Wu, H., Zhang, P., Zhou, J., Hu, S., Hao, J., Zhong, Z., et al. (2024). Paeoniflorin confers ferroptosis resistance by regulating the gut microbiota and its metabolites in diabetic cardiomyopathy. *Am. J. Physiol. Cell Physiol.* 326(3), C724–C741. doi:10.1152/ajpcell.00565.2023
- Sun, X., Wang, X., Zhao, Z., Chen, J., Li, C., and Zhao, G. (2021). Paeoniflorin inhibited nod-like receptor protein-3 inflammasome and NF- κ B-mediated inflammatory reactions in diabetic foot ulcer by inhibiting the chemokine receptor CXCR2. *Drug Dev. Res.* 82(3), 404–411. doi:10.1002/ddr.21763
- Tang, G., Li, S., Zhang, C., Chen, H., Wang, N., and Feng, Y. (2021). Clinical efficacy of Thoudam, T., Chanda, D., Lee, J. Y., Jung, M. K., Sinam, I. S., Kim, B. G., et al. (2023).

- Wu, J., Zhang, D., Hu, L., Zheng, X., and Chen, C. (2022). Paeoniflorin alleviates NG-nitro-L-argininemethylester(L-NAME)-induced gestational hypertension and upregulates silent information regulator 2 related enzyme 1 (SIRT1) to reduce H₂O₂-induced endothelial cell damage. *Bioengineered* 13(2), 2248–2258. doi:10.1080/21655979.2021.2024325
- Wu, Y., Huang, T., Li, X., Shen, C., Ren, H., Wang, H., et al. (2023). Retinol dehydrogenase 10 reduction mediated retinol metabolism disorder promotes diabetic cardiomyopathy in male mice. *Nat. Commun.* 14(1), 1181. doi:10.1038/s41467-023-36837-x
- Enhanced Ca²⁺-channeling complex formation at the ER-mitochondrial interface underlies the pathogenesis of alcohol-associated liver disease. *Nat. Commun.* 14(1), 1703. doi:10.1038/s41467-023-37214-4
- Tokarz, V.L., MacDonald, P.E., and Klip, A. (2018). The cell biology of systemic insulin dysfunction. *J. Cell Biol.* 217(7), 2273–2289. doi:10.1083/jcb.201802095
- Tu, J., Guo, Y., Hong, W., Fang, Y., Han, D., Zhang, P., et al. (2019). The regulatory effects of paeoniflorin and its derivative paeoniflorin-6'-O-benzene sulfonate CP-25 on

Wu, Y., Ren, K., Liang, C., Yuan, L., Qi, X., Dong, J., et al. (2009). Renoprotective effect of total glucosides of paeony (TGP) and its mechanism in experimental diabetes. *J. Pharmacol. Sci.* 109(1), 78–87. doi:10.1254/jphs.08112fp

Xie, J., Wang, M., Long, Z., Ning, H., Li, J., Cao, Y., et al. (2022). Global burden of type 2 diabetes in adolescents and young adults 1990–2019, systematic analysis of the Global Burden of Disease Study 2019. *BMJ* 379, e072385. doi:10.1136/bmj-2022-072385

Velloso, L. A., Eizirik, D. L., and Chop, M. (2013). Type 2 diabetes mellitus—an autoimmune disease? *Nat. Rev. Endocrinol.* 9(12), 750–755. doi:10.1038/nrendo.2013.131

Xie, Y., Bowe, B., Xian, H., Loux, T., McGill, J. B., and Al-Aly, Z. (2023). Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised

Villagarcía, H. G., Román, C. L., Castro, M. C., González, L. A., Ronco, M. T., Francés, D. E., et al. (2018). Liver carbohydrates metabolism, A new islet-neogenesis associated protein peptide (INGAP-PP) target. *Peptides* 101, 44–50. doi:10.1016/j.peptides.2018.

Yang,J.,Wei,Y.,Zhao,T.,Li,X.,Zhao,X.,Ouyang,X.,etal.(2022).Magnolol effectivelyamelioratesdiabeticperipheralneuropathyinmice.Phytomedicine107, 154434.doi:10.1016/j.phymed.2022.154434

Yang,X.,Li,X.,Zhu,Y.,Gao,Y.,andXu,L.(2022).Paeoniflorinupregulates

Zhang, L., Peng, C. Y., Wang, P. X., Xu, L., Liu, J. H., Xie, X., et al. (2023c). phytochemical profiles of the ethyl acetate fraction from *Radix Paeoniae Alba*. *Front. Nutr.* 10, 1126359. doi:10.3389/fnut.2023.1126359

Hypoglycemic and H₂O₂-induced oxidative injury protective effects and the

mitochondrial thioredoxin of Schwann cells to improve diabetic peripheral neuropathy indicated by 4D label-free quantitative proteomics. *Oxid. Med. Cell Longev.* 2022, 4775645. doi:10.1155/2022/4775645

Zhang, L., and Wei, W. (2020). Anti-inflammatory and immunoregulatory effects of paeoniflorin and total glucosides of paeony. *Pharmacol. Ther.* 207, 107452. doi:10.1016/j.pharmthera.2019.107452

Yang, X., Yao, W., Li, Q., Liu, H., Shi, H., Gao, Y., et al. (2015). Mechanism of Tang Luo Ning effect on attenuating oxidative stress in sciatic nerve of STZ-induced diabetic rats. *J. Ethnopharmacol.* 174, 1–10. doi:10.1016/j.jep.2015.07.047

- Zhang, M.H., Feng, L., Zhu, M.M., Gu, J.F., Wu, C., and Jia, X.B. (2013). Antioxidative and anti-inflammatory activities of paeoniflorin and oxypaeoniflorin in AGEs-induced mesangial cell damage. *Planta Med.* 79 (14), 1319–1323. doi:10.1055/s-0033-1350649
- Yang, X., Yao, W., Shi, H., Liu, H., Li, Y., Gao, Y., et al. (2016). Paeoniflorin protects Schwann cells against high glucose induced oxidative injury by activating Nrf2/ARE pathway and inhibiting apoptosis. *J. Ethnopharmacol.* 185, 361–369.
- Yao, M., Li, L., Huang, M., Tan, Y., Shang, Y., Meng, X., et al. (2021). Sanyetab tablet ameliorates insulin resistance and dysregulated lipid metabolism in high-fat diet-induced obese mice. *Front. Pharmacol.* 12, 713750. doi:10.3389/fphar.2021.713750
- Yeom, E., Byeon, H., and Lee, S.J. (2016). Effect of diabetic duration on hemorheological properties and platelet aggregation in streptozotocin-induced diabetic rats. *Sci. Rep.* 6, 21913. doi:10.1038/srep21913
- Zhang, T., Ouyang, H., Mei, X., Lu, B., Yu, Z., Chen, K., et al. (2019). Erianin alleviates diabetic retinopathy by reducing retinal inflammation initiated by microglial cells via
- Yu, H., Gong, W., Mei, J., Qin, L., Piao, Z., You, D., et al. (2022). The efficacy of a paeoniflorin-sodium alginate-gelatin skin scaffold for the treatment of diabetic wound, an in vivo study in a rat model. *Biomed. Pharmacother.* 151, 113165. doi:10.1016/j.

(11),11776–11790.doi:10.1096/fj.201802614RRR

Zhang,T.,Zhu,Q.,Shao,Y.,Wang,K.,andWu,Y.(2017).Paeoniflorinprevents TLR2/4-mediatedinflammation intype 2diabeticnephropathy.Biosci.Trends11 (3), 308–318.doi:10.5582/bst.2017.01104

Zhang, W., Zhao, L., Su, S. Q., Xu, X. X., andWu, Y. G. (2014). Total glucosidesof paeonyattenuaterenal tubulointerstitialinjuryinSTZ-induceddiabeticrats,roleof Toll-likereceptor2.J.Pharmacol.Sci.125(1),59–67.doi:10.1254/jphs.13173fp

Zhang,X.,Yin,H.,Zhang,X.,Jiang,X.,Liu,Y.,Zhang,H.,etal.(2022b).N6-methyladenosinemodificationgoverns liverglycogenesisbystabilizingtheglycogen synthase2mRNA.Nat.Comm.13(1),7038.doi:10.1038/s41467-022-34808-2

Yu, L. M., Dong, X., Xue, X. D., Xu, S., Zhang, X., Xu, Y. L., et al. (2021). Melatonin attenuates diabetic cardiomyopathy and reduces myocardial vulnerability to ischemia-reperfusion injury by improving mitochondrial quality control, Role of SIRT6. J. Pineal Res.70(1),e12698.doi:10.1111/jpi.12698

Yue,T.,Shi,Y.,Luo,S.,Weng,J.,Wu,Y.,andZheng,X.(2022).Theroleof inflammationinimmunesystemofdiabeticretinopathy,Molecularmechanisms, pathogeneticroleandtherapeuticimplications.Front.Immunol.13,1055087. doi:10.3389/fimmu.2022.1055087

Zeng,K.,Xi,W.,Qiao,Y.,Huang,X.,andLiu,X.(2022).Paeoniflorininhibits epithelial mesenchymal transformation and oxidative damage of lens epithelial cells in diabetic cataract via sirtuin 1 upregulation. Bioengineered 3 (3), 5903–5914. doi:10.1080/ 21655979.2021.2018534

Zhai,T.,Sun,Y.,Li,H.,Zhang,J.,Huo,R.,Li,H.,etal.(2016).Unique immunomodulatoryeffectofpaeoniflorinontypelandII macrophagesactivities. J.Pharmacol.Sci.130(3),143–150.doi:10.1016/j.jphs.2015.12.007

Zhang, B., Li, F. J., Liu, X. Z., and Zuo, Z. F. (2023a). Paeoniflorin inhibits retinal cell inflammationindiabetesratsbasedonJAK2/STAT3signalingpathway.Chin. J.Ophthalmol.33(04),305–310.doi:10.13444/j.cnki.zgzykzz.2023.04.002

Zhang, B., Li, F. J., and Zuo, Z. S. (2019). Protective effects of paeoniflorin on retinal Müller cells of diabetic rats. Chin. J. Ophthalmol. 29 (01), 5–9. doi:10.19879/j.cnki.1005-

- Zhang, Y., Li, Y., Li, C., Zhao, Y., Xu, L., Ma, S., et al. (2023d). Paeonia × suffruticosa Andrews leaf extract and its main component apigenin 7-O-glucoside ameliorate hyperuricemia by inhibiting xanthine oxidase activity and regulating renal urate transporters. *Phytomedicine* 118, 154957. doi:10.1016/j.phymed.2023.154957
- Zhang, Y., Liang, Y., Liu, H., Huang, Y., Li, H., and Chen, B. (2020). Paeoniflorin attenuates gestational diabetes via Akt/mTOR pathway in a rat model. *Food Nutr. Res.* 64:doi:10.29219/fnr.v64.4362
- Zheng, X., Ke, Y., Feng, A., Yuan, P., Zhou, J., Yu, Y., et al. (2016). The mechanism by which amentoflavone improves insulin resistance in HepG2 cells. *Molecules* 21 (5), 624. doi:10.3390/molecules21050624
- Zhong, B. L., He, S. Q., Sun, H. T., Chen, W. C., Zhang, M. J., Zhong, X. D., et al. (2023). Paeoniflorin coordinates macrophage polarization and mitigates liver inflammation and fibrogenesis by targeting the NF- κ B/HIF-1 α pathway in CCl₄-induced liver fibrosis. *Am. J. Chin. Med.* 51(5), 1249–1267. doi:10.1142/S0192415X2350057X
- Zhou, X., Fouda, S., Zeng, X. Y., Li, D., Zhang, K., Xu, J., et al. (2019). Characterization of the therapeutic profile of albiflorin for the metabolic syndrome. *Front. Pharmacol.* 10, 1151. doi:10.3389/fphar.2019.01151
- Zhou, Y. X., Gong, X. H., Zhang, H., and Peng, C. (2020). A review on the pharmacokinetics of paeoniflorin and its anti-inflammatory and immunomodulatory effects. *Biomed. Pharmacother.* 130, 110505. doi:10.1016/j.biopha.2020.110505
- Zhang, L., Deng, M., Wang, S. Y., Ding, Q., Liu, J. H., Xie, X., et al. (2023b). Mitigation of Paeoniae Radix Alba extracts on H₂O₂-induced oxidative damage in HepG2 cells and hyperglycemia in zebrafish, and identification of phytochemical constituents. *Front. Nutr.* 10, 1135759. doi:10.3389/fnut.2023.1135759
- Zhang, L., Han, L., Ma, J., Wu, T., Wei, Y., Zhao, L., et al. (2022a). Exploring the synergistic and complementary effects of berberine and paeoniflorin in the treatment of type 2 diabetes mellitus by network pharmacology. *Eur. J. Pharmacol.* 919, 174769.

Zhu, S. H., Liu, B. Q., Hao, M. J., Fan, Y. X., Qian, C., Teng, P., et al. (2017). Paeoniflorin suppressed high glucose-induced retinal microglia MMP-9 expression and inflammatory response via inhibition of TLR4/NF- κ B pathway through upregulation of SOCS3 in diabetic retinopathy. *Inflammation* 40(5), 1475–1486. doi:10.1007/s10753-017-0571-z

Zhu, Y., Han, S., Li, X., Gao, Y., Zhu, J., Yang, X., et al. (2021). Paeoniflorin effect of Schwann cell-derived exosomes ameliorates dorsal root ganglion neurons apoptosis through IRE1 α pathway. *Evid. Based Complement. Altern. Med.* 2021, 6079305. doi:10.1155/2021/6079305